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THE AMERICAN JOURNAL OF ROENTGENOLOGY RADIUM THERAPY AND NUCLEAR MEDICINE

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JANUARY, 1968 NUMBER 1

'eth Annual Meeting, American Radium Society
Hotel Fontainebleau, Miami Beach, Florida
April 7-11, 1968
PRELIMINARY PROGRAM

4 of every 5 new Departments of Nuclear Medicine get started with a Magnascanner®

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More. In less than 10 years the Magnascanner has become the keystone instrument in most Departments of Nuclear Medicine. This was the instrument that helped Nuclear Medicine specialists develop radioisotope diagnosis from a limited research technique to a practical, valuable, everyday, reliable, routine methodology. And in this rapidly-changing decade, the instrument changed too: multiple improvements and options were (and are always being) incorporated, making this the most up-to-date scanner available. Simultaneously, our line of other instruments for Nuclear Medicine expanded to the point of being the widest around. Nevertheless, nothing *anyone* has been able to do in this area (ourselves or others) has served to dislodge the Magnascanner from its keystone position in most Radioisotope Departments.

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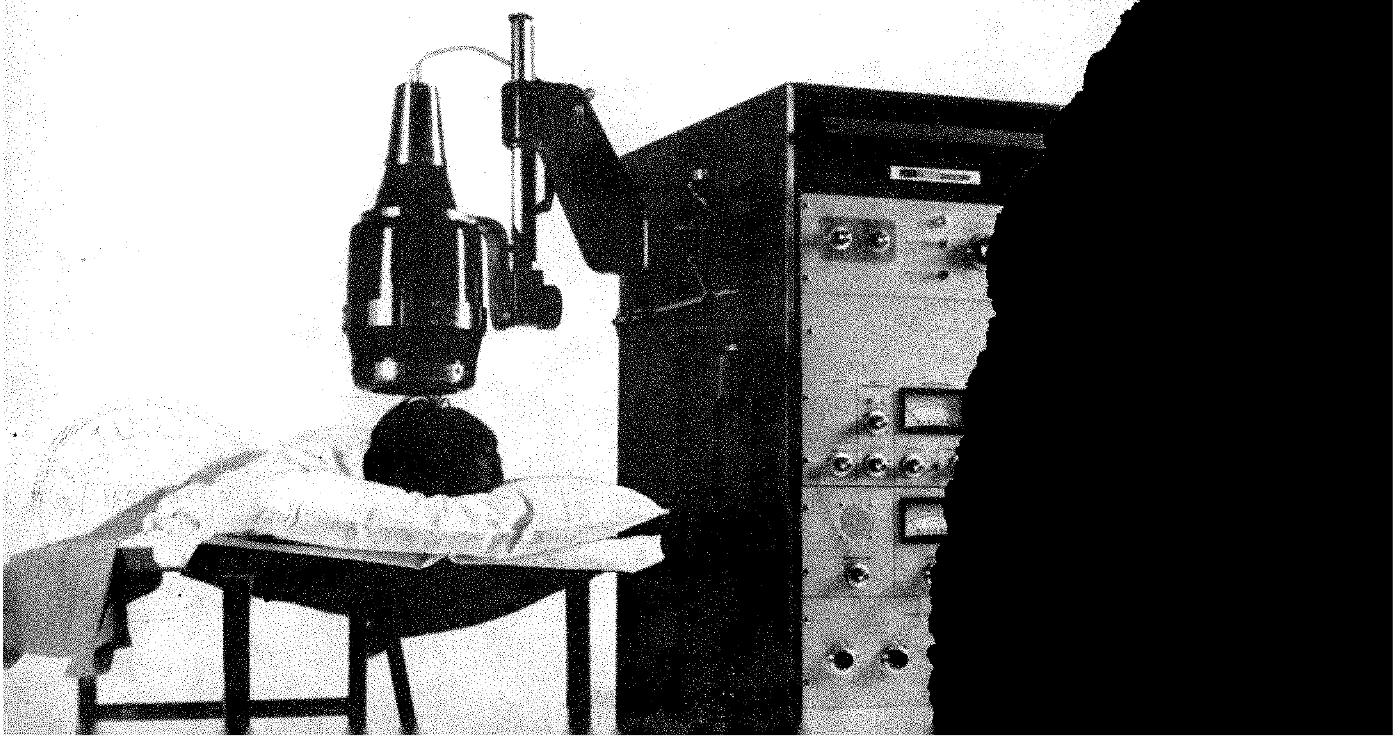

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SQUIBB

a research concep… …har…

New help in diagnosing pulmonary problems

New radioisotope scanning procedure can help detect the vascular changes of pulmonary disease before they show on chest films

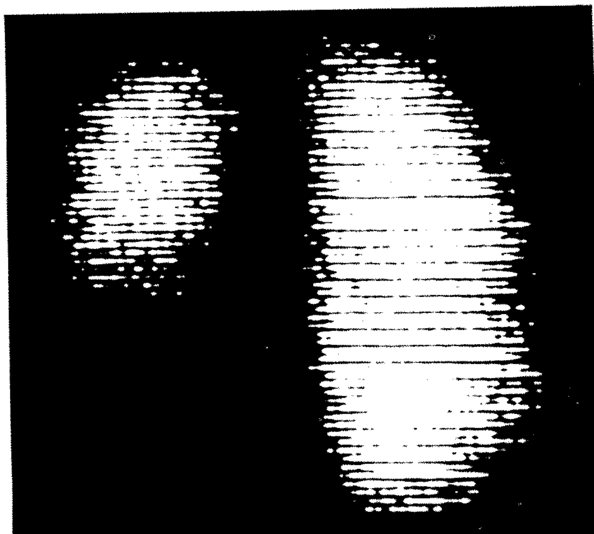
Scintiscanning of the lungs now offers a new approach to the diagnosis of pulmonary disease.[1] With use of macroaggregated radio-iodinated I^{131} albumin, lung scanning has been found to be simple, rapid and relatively safe,[2,3] and is invaluable as an adjunct to other diagnostic procedures whenever information about pulmonary vasculature is desired.

Perhaps the most useful application of the lung scan has been for the early detection of pulmonary embolism where "... it appears that the lung scan can point to the site of embolic lesions before signs of lung infarction are recognizable on plain chest films."[3] This is important, for with the development of new means of treating pulmonary embolism, the need for improved diagnostic ability has increased. For example, the availability of anticoagulant drugs to prevent further thrombosis and of proteolytic agents to dissolve thrombi already formed, the use of surgical therapy (such as ligation or plication of the inferior vena cava and even pulmonary embolectomy) – all require more accurate diagnostic procedures.[4,5]

Of course, pulmonary arteriography can give an immediate positive demonstration of an obstruction in the pulmonary circulation as soon as it occurs, but this procedure is time consuming and technically difficult to perform. It necessitates injection of large quantities of high density contrast medium directly into the pulmonary artery, and it also requires cardiac catheterization (with some risk of dislodgement of venous thrombi). Moreover, experience has shown that patients with pulmonary hypertension may tolerate injections of contrast material poorly. Other examinations, such as x-ray study of the chest and electrocardiography, are rarely definitive.[4]

In contrast, lung scanning with Albumotope-LS is a simple and direct adjunctive measure; reliable and virtually without risk of morbidity to the patient. And unlike pulmonary arteriography it does not require cardiac catheterization and involves only minimal inconvenience to the patient. All that is required is the i.v. administration of a relatively small amount of the isotope. And the test may be supplemented with other procedures when necessary.

Although the lung scan has been used most frequently for the detection of pulmonary emboli, it can provide useful information in the diagnosis and evaluation of other pulmonary problems. For example, a recent report[6] in the September, 1966, issue of *Circulation* discusses the potential applicability of the technique in the detection and assessment of mitral valve disease. According to the authors, the technique has been found useful in screening patients with clinical findings of mitral valve disease who were not considered symptomatic enough to warrant cardiac catheterization... in the preoperative study of patients so ill that left heart catheterization was unusually hazardous... and in determining whether the pulmonary venous pressure is elevated in patients with known severe pulmonary arterial hypertension. In these latter patients it is often difficult to measure pulmonary arterial wedge pressure reliably and the more extensive manipulations necessary for left heart catheterization may be poorly tolerated. Thus, assessment of the distribution of pulmonary arterial blood flow by lung scanning affords a means for determining the existence of pulmonary venous hypertension, which suggests the presence of potentially correctable lesions, such as mitral stenosis or cor triatriatum.[6]



Photoscan of lungs of female patient, aged 50, showing pulmonary emboli. Chest x-ray taken same day showed no radiographic evidence of pulmonary embolism.*

Albumotope®-LS

Squibb Aggregated Radio-Iodinated (I^{131}) Albumin (Human)

References:
(1) Quinn, J. L., III; Whitley, J. E.; Hudspeth, A. S., and Prichard, R. W.: Radiology *82*:315 (Feb.) 1964. (2) Sabiston, D. C., Jr., and Wagner, H. N., Jr.: Ann. Surg. *160*:575 (Oct.) 1964. (3) Haynie, T. P.; Hendrick, C. K., and Schreiber, M. H.: J. Nucl. Med. 6:613, 1965. (4) Wagner, H. N., Jr., *et al.*: New Eng. J. Med. *271*:377 (Aug. 20) 1964. (5) Quinn, J. L., III; Whitley, J. E.; Hudspeth, A. S., and Watts, F. C.: J. Nucl. Med. 5:1 (Jan.) 1964. (6) Friedman, W. F., and Braunwald, E.: Circulation *34*:363 (Sept.) 1966.

Dosage and Scanning Procedure: Recommended scan doses of 150 to 300 microcuries of aggregated radioiodinated (I^{131}) albumin depending on the instrumentation available and the technics employed. Scanning immediately follows administration of slow intravenous injection. Patient may be placed in a prone or supine position.

Side Effects and Precautions: Radioisotopes should not be used in pregnant women, nursing mothers, or in patients under 18 years of age unless indications are very exceptional.

There have been no reported cardiovascular or other untoward effects attributable to Albumotope-LS. Extensive clinical use of Albumotope-LS has not borne out the hypothetical possibility that particles of large size might induce deleterious cardiovascular or cerebrovascular effects. The product appears to possess no antigenic properties. One patient with a known history of angioneurotic edema, who had been given Lugol's solution in conjunction with aggregated radioalbumin similar to Albumotope-LS, developed urticaria.

Available: As a sterile, non-pyrogenic, aqueous suspension. Each cc. contains approximately 1 mg. aggregated human serum albumin labeled with 800-1500 microcuries of iodine-131 at time of manufacture. Also contains 0.9% benzyl alcohol as a preservative.

*Illustration furnished through the courtesy of George V. Taplin, M.D., Harbor General Hospital, Torrance, California.

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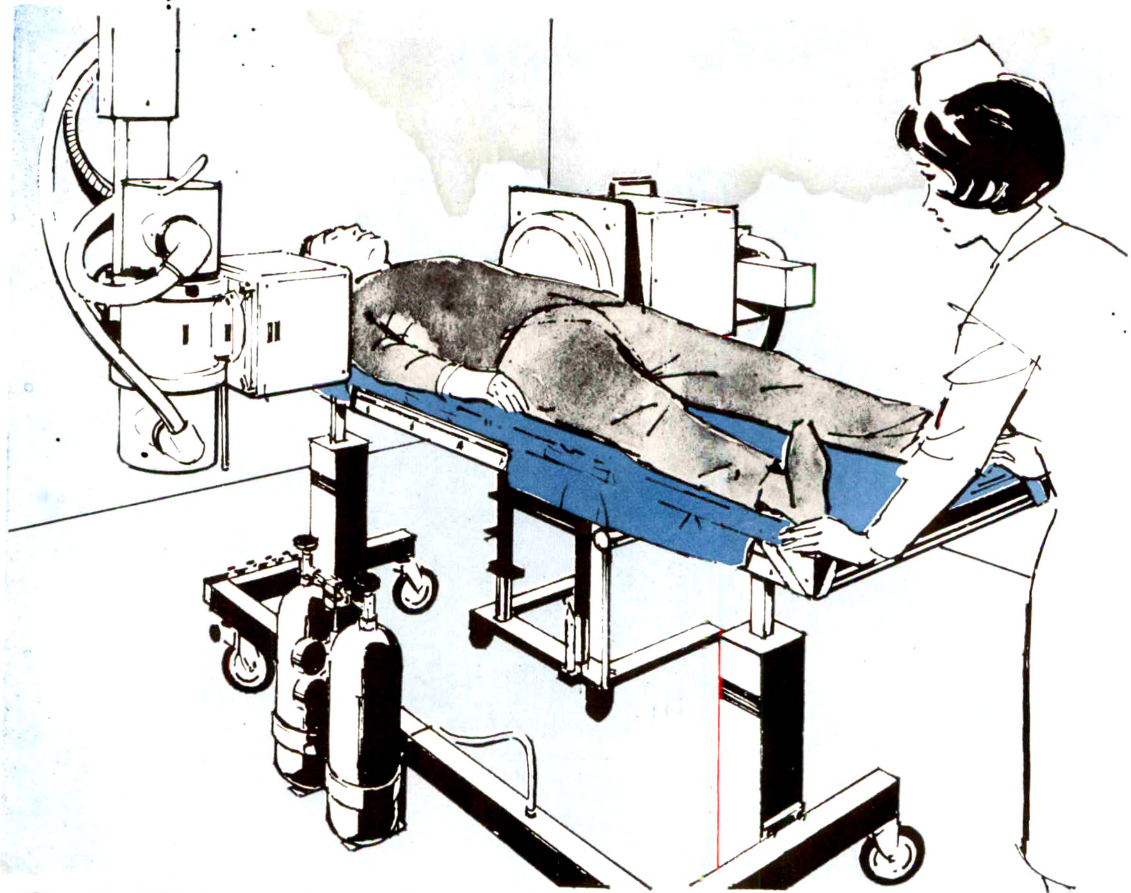

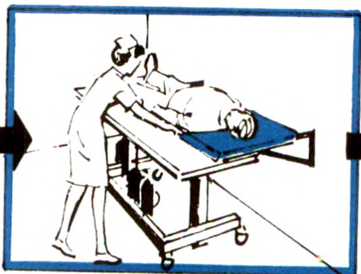

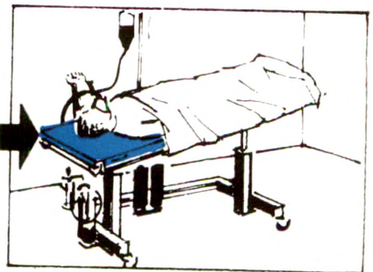

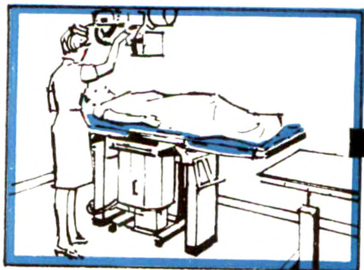

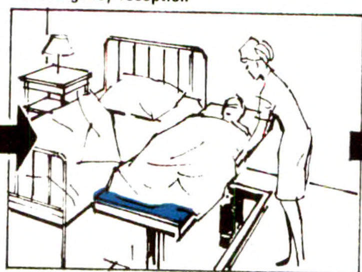

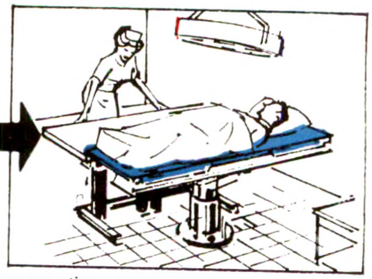

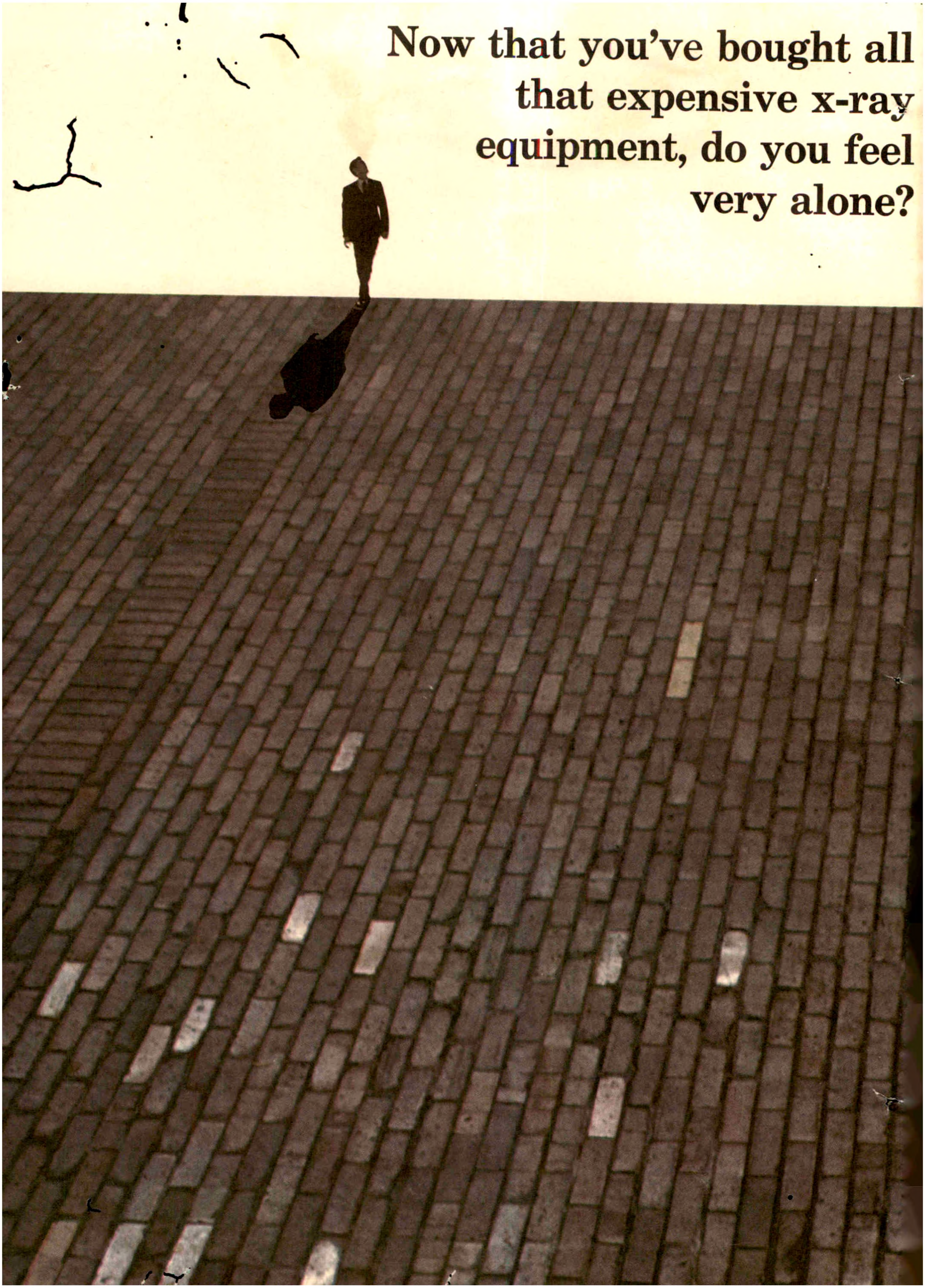
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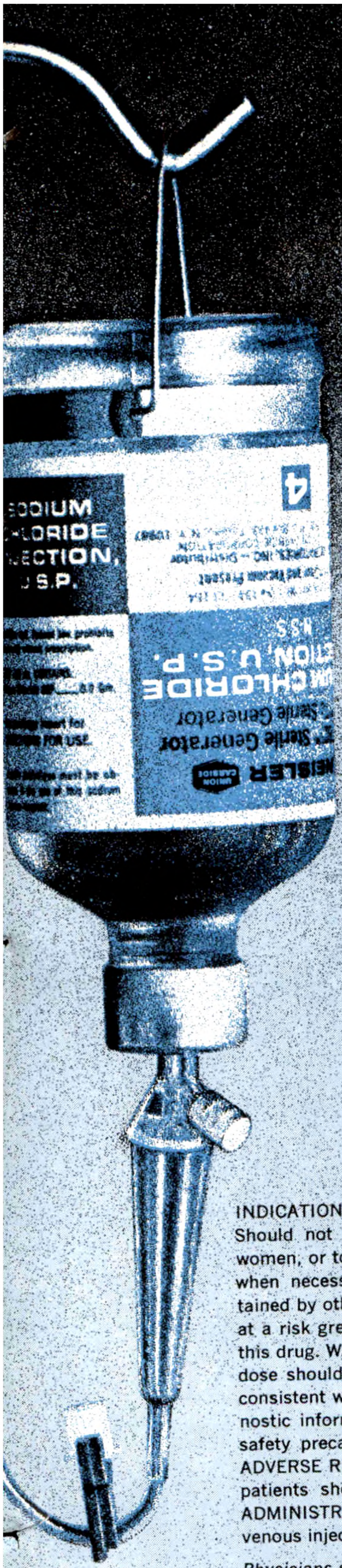

Diagnostic Problem:

When
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- **Infancy**
- **Advanced age**
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Side Effects: Excretory urographic agents may produce symptoms of an anaphylactic* nature in sensitive persons. Patients should be watched carefully during injection as serious reactions, including fatalities, have occurred with all commonly used mediums. Although allergic reactions generally occur quickly, occasionally they may not be manifested for 10 or even 15 minutes. Warning signs and symptoms of possible intolerance or allergy include respiratory difficulty (wheezing, dyspnea or sensation of suffocation, and tightness in the throat or chest), sneezing, itching or urticaria, nausea or vomiting, and fainting. Minor reactions, such as nausea, vomiting, excessive salivation, flushing, dizziness, urticaria, and muscular twitching may occur. Special care is advisable in persons with a history of bronchial asthma or other allergic manifestations of sensitivity, especially to iodine. Infrequently "iodism" (Salivary gland swelling) appears two days after exposure and subsides by the sixth day. In euthyroid patients following excretory urography with Hypaque, protein-bound iodine is elevated and the thyroid I^{131} uptake is lowered, returning to normal after the 3rd and 4th day respectively.

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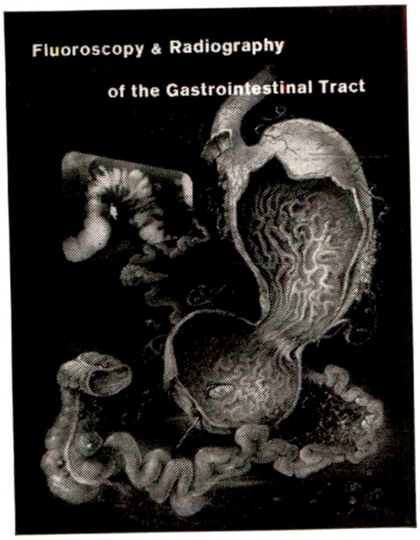

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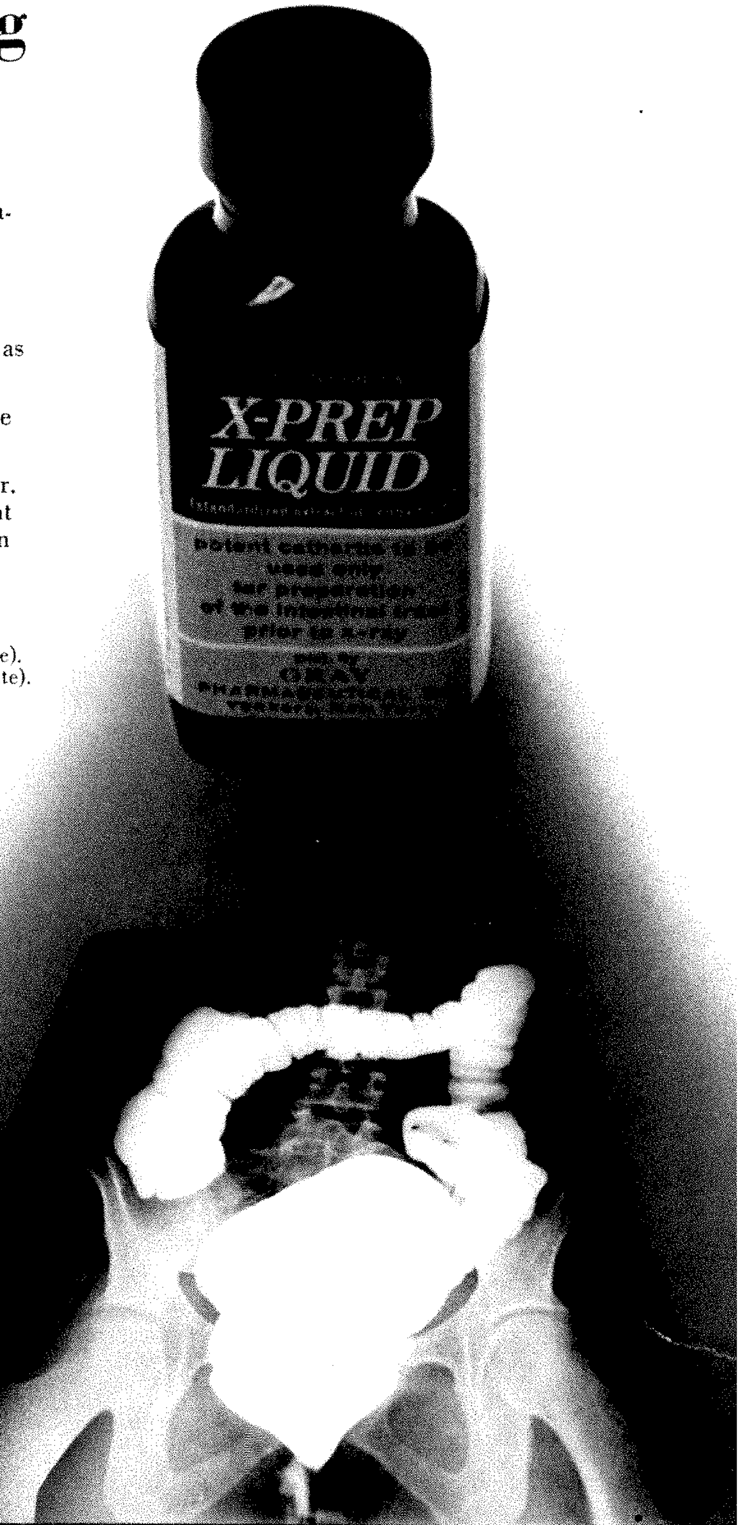

X-ray visualization following barium enema. Patient prepared with single dose of X-PREP Liquid—2½ oz. Note absence of fecal retention. Courtesy of Statman, A. J.: An Effective Single-Dose Evacuant, J. M. Soc. New Jersey 63:95 (March) 1966.

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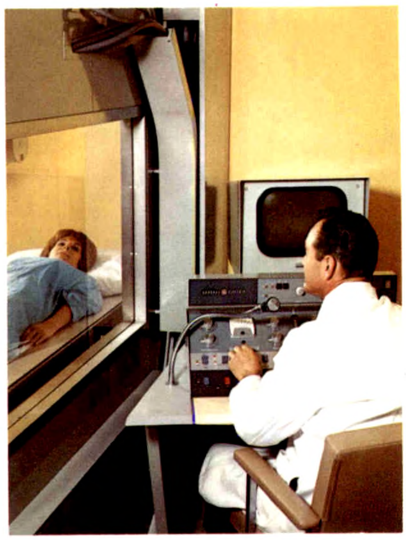

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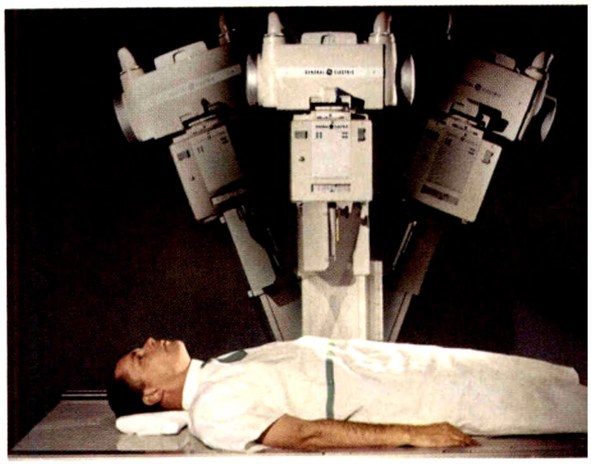

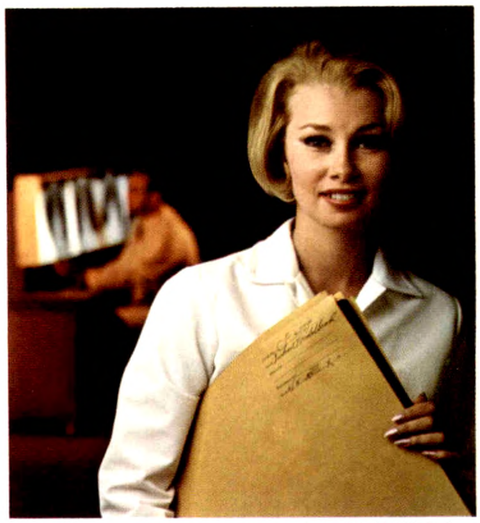

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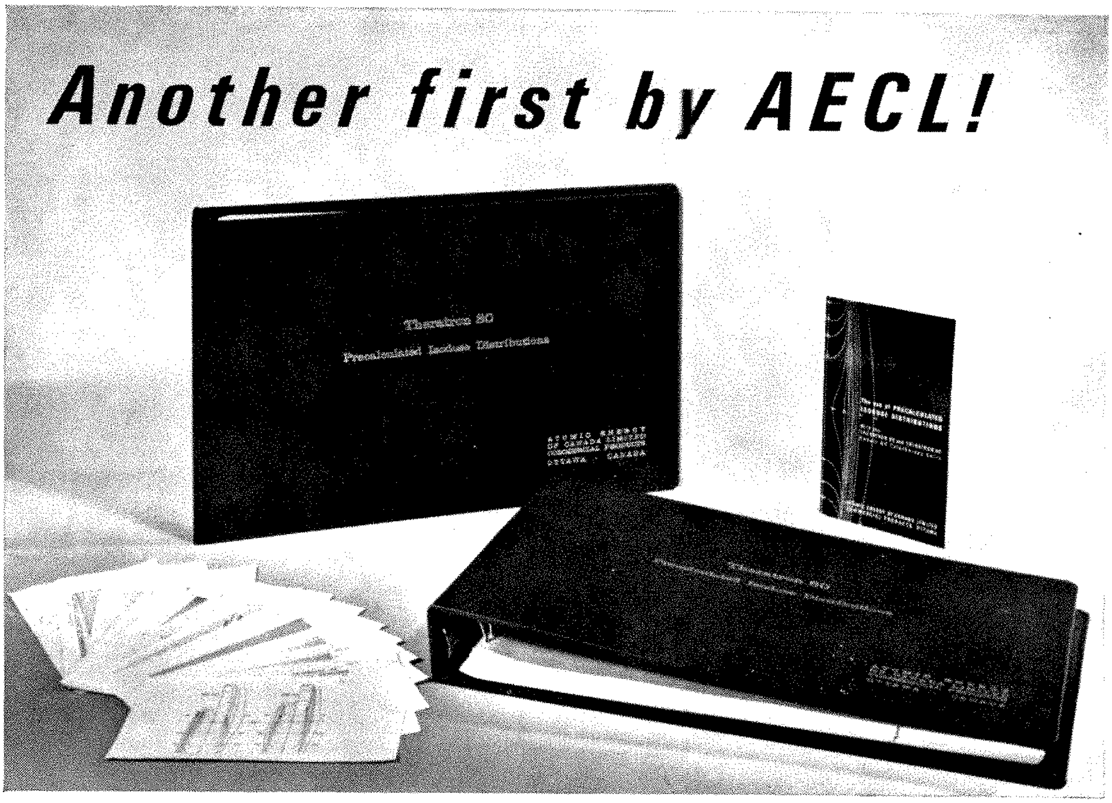

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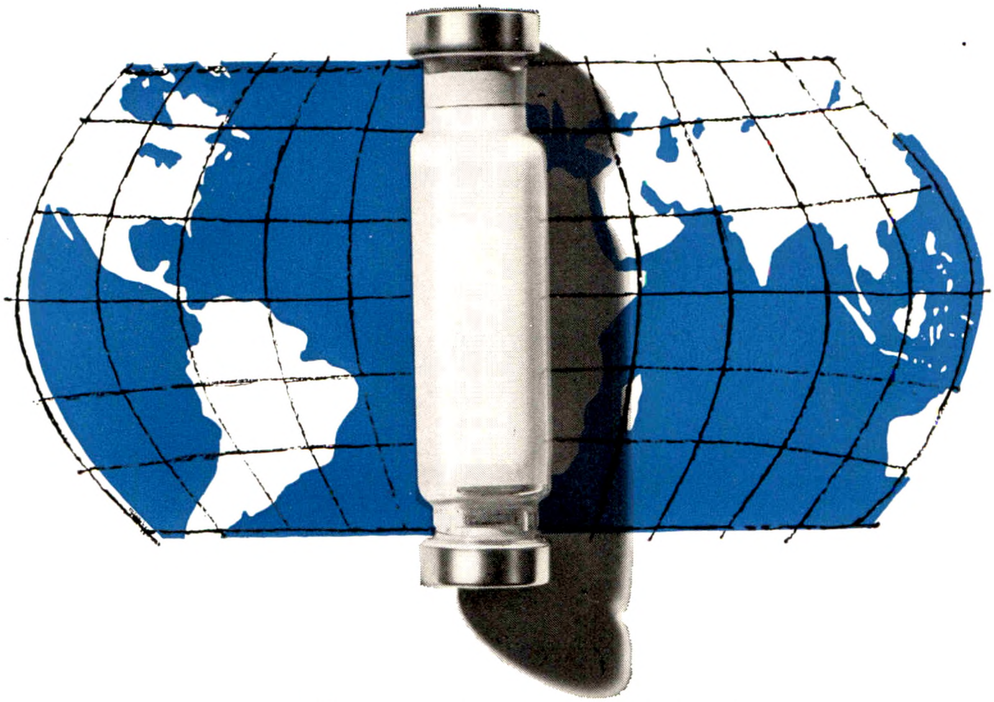

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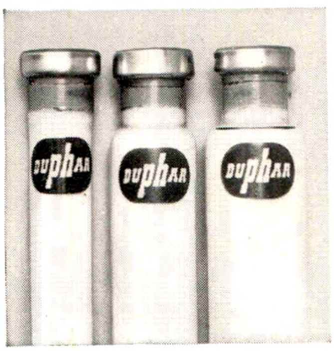

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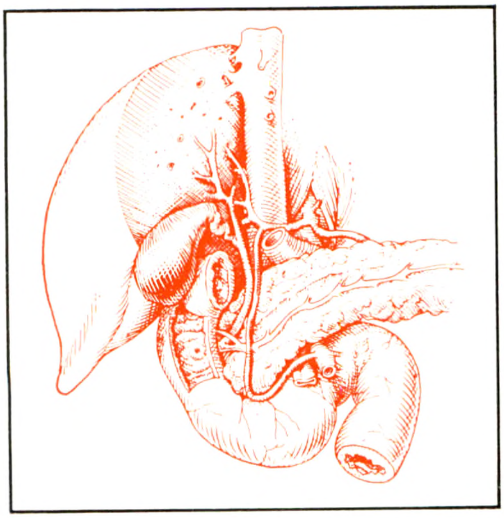

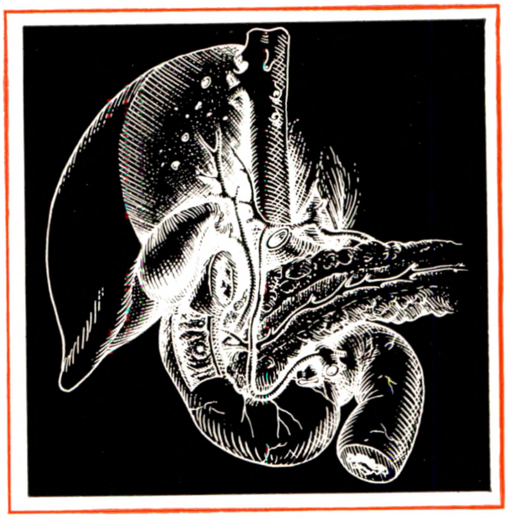

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definition of maximum concentration

high absorption index—"No one will dispute the statement that the diagnostic reliability of oral cholecystography depends upon the degree of absorption of the contrast medium employed."[1] Radioisotope studies with ipodate sodium show a markedly improved absorption index (approximately 70 per cent) with no increase in the toxic properties.[1]

less bowel residue—"Incomplete and variable absorption of a cholecystographic agent is not desirable, for the opacification of the gallbladder is then less dependent on the status of the gallbladder and more a reflection of the percentage absorption."[2] "Opaque material in the bowel was found in 46 per cent of [105 patients in] the... [iopanoic acid] group as compared with 9 per cent of those [99] of the [Oragrafin Sodium Capsules]...group."[2] In another study, 49 of 100 patients receiving iopanoic acid had residue in the gastrointestinal tract, while only 15 of 100 patients receiving Oragrafin had such residue.[3]

excellent opacification—"In addition to its ease of administration and safety, its principal advantages are a high yield of diagnostic films...."[4]

definition of better toleration

low incidence of untoward reactions—In contrast to findings with other cholecystographic agents, Lewitan and Garcia[5] reported in their 246 patient study: "With

ipodate calcium...there was no clinical evidence of immediate or delayed nephrotoxicity in any of the patients given it...."[5] To study possible renal toxicity, "Creatinine clearance tests were also done before and after administration of multiple doses in excess of 6 gm. in 8 cases, and showed no significant alterations."[5] However, "Multiple doses beyond 6 gm. are not recommended."[5] In their study of 120 patients, Glenn and O'Brien reported "...no reactions in this series of patients attributable to the administration of [Oragrafin]...."[4] And, McCrory reported that Oragrafin was "...used routinely in cholecystographic studies in approximately 2000 patients with excellent diagnostic films and only rare and mild reactions."[6]

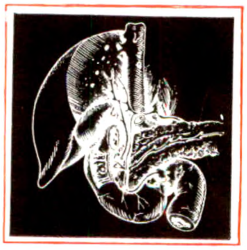
side effects compared to iopanoic acid

side effects encountered in administration of 3 Gm. of Oragrafin Sodium Capsules and 3 Gm. iopanoic acid*

	Oragrafin Sodium Capsules (Squibb Sodium Ipodate)	iopanoic acid
no. of cases	99	105
no. of side effects		
nausea		
slight	10	14
severe	2	6
vomiting	0	1
diarrhea		
mild	7	22
severe	3	16
cramps	5	15
dysuria	9	13
total/per cent	36 (36.3%)	87 (82.9%)

*Adapted from White, W. W., and Fischer, H. W.[2]

Juhl,[3] in his study of 200 patients (100 on each agent), found no significant difference between iopanoic acid and sodium ipodate in the incidence of nausea; vomiting occurred in an equal number of cases.



definition of convenience:

Oragrafin® Calcium Granules

Squibb Calcium Ipodate

visualization of poorly functioning gallbladder reduces the need for I.V. studies—In a concentrating gallbladder, Oragrafin Calcium Granules (Squibb Calcium Ipodate) will show storage, concentration, delivery or stones. A patent biliary duct can generally be expected to visualize. Provided the cystic duct is patent, Oragrafin will visualize the normal gallbladder, the abnormal gallbladder containing papillomata, nonopaque stones or radiodense calculi, and gallbladders where concentrating power is diminished.

patient convenience—Routine cholecystography night-before procedure is easy for patients to follow; palatable granules further enhance patient acceptability. Rapid clearance of medium permits same-day administration and gallbladder and ductal films, and, if necessary, same-day re-examination; reduces need for I.V. studies.

Optimal concentration in the hepatic and biliary ducts usually occurs within 1 to 3 hours. Although the gallbladder is optimally opacified 10 hours after ingestion of the agent, diagnostically valuable information can often be obtained within 5 hours or less.

rapid absorption permits same-day re-examination—To determine the cause of nonopacification after routine cholecystography, most physicians require re-examination by repeating the procedure at a later date (sometimes doubling dose), or

A 2893

by administering more agent the evening of the first unsuccessful examination (again sometimes doubling dose), and repeating the study the next day. "The advantage of the calcium ipodate method is that the examination can be completed in five additional hours with a limited dose of contrast agent."[7]

a valuable medium for peroral cholegraphy[5]—Rapidly absorbed from the gastrointestinal tract, calcium ipodate has been reported by some investigators to be diagnostically superior to other oral cholangiographic contrast agents. With careful timing of the examination and the use of tomograms or laminograms, the frequency of good results can approximate that obtained with intravenously administered agents. According to Lewitan and Garcia,[5] the medium's relative safety makes it a valuable medium for peroral cholegraphy. Timesaving and economical Oragrafin Calcium Granules may be particularly useful in certain patients for whom I.V. radiography presents potential hazards, such as elderly patients, those with cardiovascular disease, or patients who may exhibit sensitivity to the test dose of an intravenous agent.

Unique among oral media, Oragrafin Calcium Granules permits same-day films of the gallbladder and ductal system.

dosage schedule for films of gallbladder and ductal system

8 A.M.	2 packets of granules
9 A.M.	visualization of ducts
10 A.M.	optimal visualization of ducts
1 P.M.	visualization of gallbladder

References: 1. Sanen, F. J.: Amer. J. Roentgen. *88*:797 (Oct.) 1962. **2.** White, W. W., and Fischer, H. W.: Amer. J. Roentgen. *87*:745 (April) 1962. **3.** Juhl, J. H., *et al.*: Radiology *80*:87 (Jan.) 1963. **4.** Glenn, J. C., Jr., and O'Brien, P. S.: Southern Med. J. *56*:167 (Feb.) 1963. **5.** Lewitan, A., and Garcia, J. F.: Amer. J. Dig. Dis. *10*:219 (March) 1965. **6.** McCrory, E.: J. Tenn. Med. Ass. *58*:258 (Aug.) 1965. **7.** Crummy, A. B.: Wisconsin Med. J. *65*:84 (Feb.) 1966.

Contraindications: Contraindicated for persons sensitive to oral iodine compounds or for patients with combined renal and hepatic disease or severe kidney impairment. Gastrointestinal disorders, which may interfere with absorption, or liver dysfunction, which may result in inadequate biliary secretion of medium, are likely to result in unsatisfactory visualization.

Precautions and Side Effects: Mild and transient nausea, vomiting, or diarrhea sometimes occur; but the incidence can be reduced by using the calcium granules and restricting the dosage to 3 Gm. Transient headache, dysuria, or abdominal pains may occur.

Hypersensitivity reactions may include urticaria, serum sickness-like reactions (fever, rash, arthralgia), other skin reactions, and rarely anaphylactoid shock. They are more likely to occur in the individual with a history of allergy, asthma, hay fever, or urticaria and in the individual who is known to be hypersensitive to iodine compounds. Antihistamines and corticosteroids are used to control hypersensitivity reactions; but the occasional serious anaphylactoid reactions require the immediate use of epinephrine or phenylephrine, oxygen, and intravenous corticosteroids.

For full information see Package Insert.

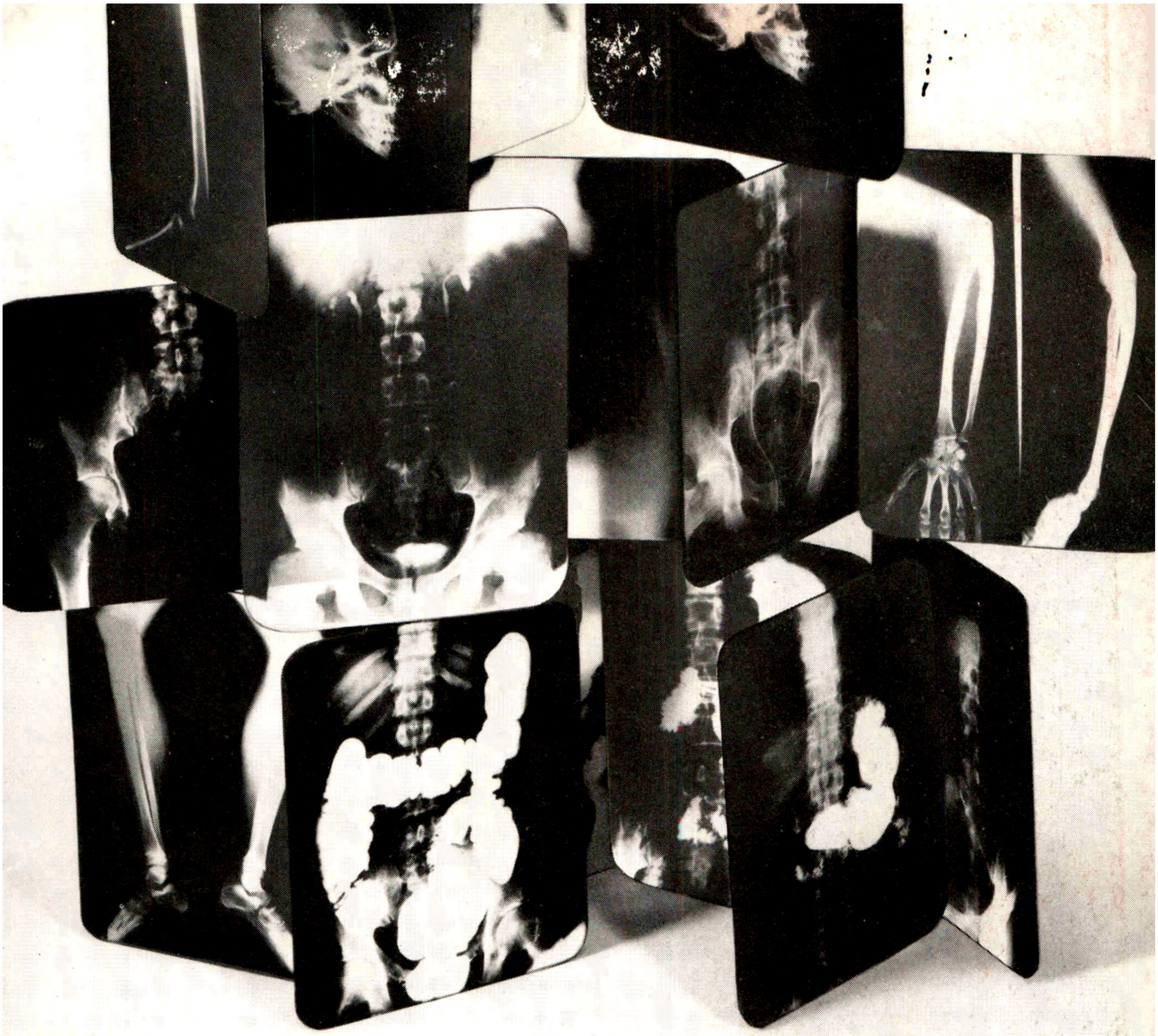
Supply: The *calcium* salt (Oragrafin Calcium Granules) is available in single-dose foil packets providing 3 Gm. of calcium ipodate as Granules dispersed in flavored sucrose. The *sodium* salt is available in capsule form (Oragrafin Sodium Capsules) providing 0.5 Gm. sodium ipodate per capsule.

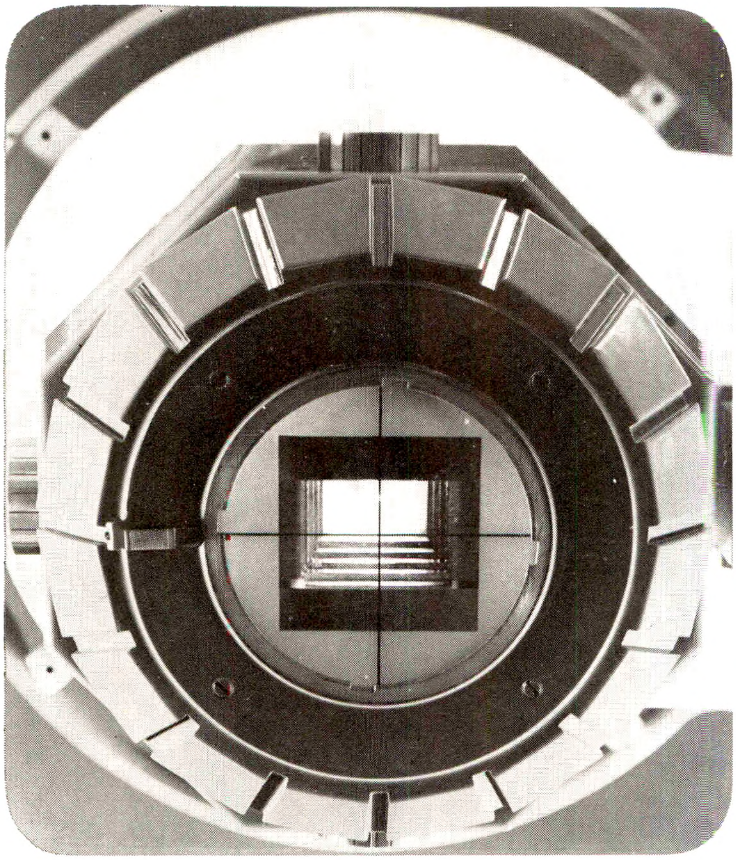
in oral cholangiography and cholecystography

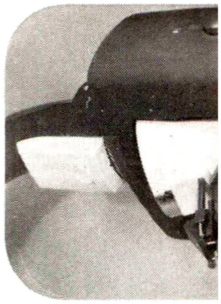
Oragrafin®

Squibb Ipodate

for maximum concentration with better patient toleration







JUST A D

-BUT IT

LARG

Cobalt 60

Life would be much easier for a lot of people if a Cobalt 60 source could be made infinitesimally small; unfortunately this is not the case. Hence the designer of a therapy unit is faced with a problem viz. penumbra... yet the radiotherapist must be able to deliver an optimum dose to the tumour and at the same time spare as much of the surrounding tissue as possible. As we see no future in passing our problems on to our clients, Philips design experts have gone to the utmost limits of precision engineering in building the diaphragm for the Philips Cobalt 60 unit itself.

Of the various feasible types, the obvious choice for Philips was the focussed one. It limits the beam so sharply that unwanted rays impinge on a uniform quantity of protective material (lead and tungsten lamellae) which almost completely absorbs them. It is more complicated to make than a simple block diaphragm, but it cannot be ignored by any one whose aim is peak efficiency.

The important - and exclusive - feature of the Philips design is that the lamellae are focussed on two diametrically opposed points on the edge of the source. Consequently no matter what field size has been set, the total surface of the source contributes to the exposure rate decided on for irradiating the tumour, irrespective of its size.

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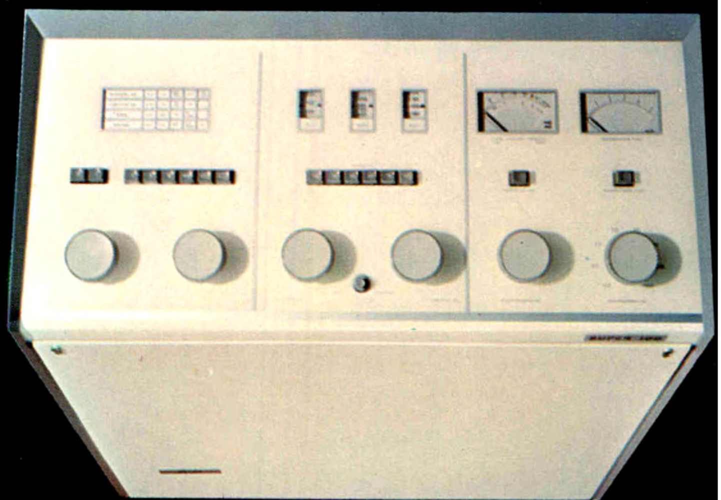

hree Phase Generator Systems deliver important advantages for efficient ys: optimum tube loading (MAS system) under all circumstances, shortest xposure times, with "falling load" for automatic density control. Only one ection is necessary: KV. Press the exposure button, Norelco generators

THE X-RAY TUBE, OPTIMUM LOADING

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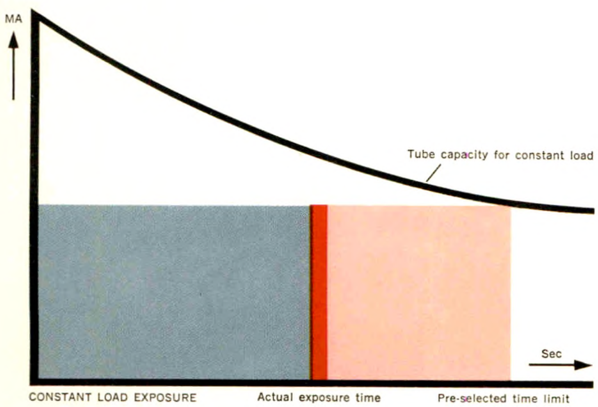
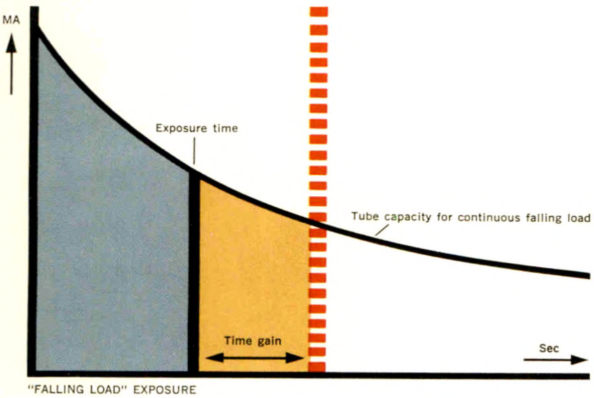
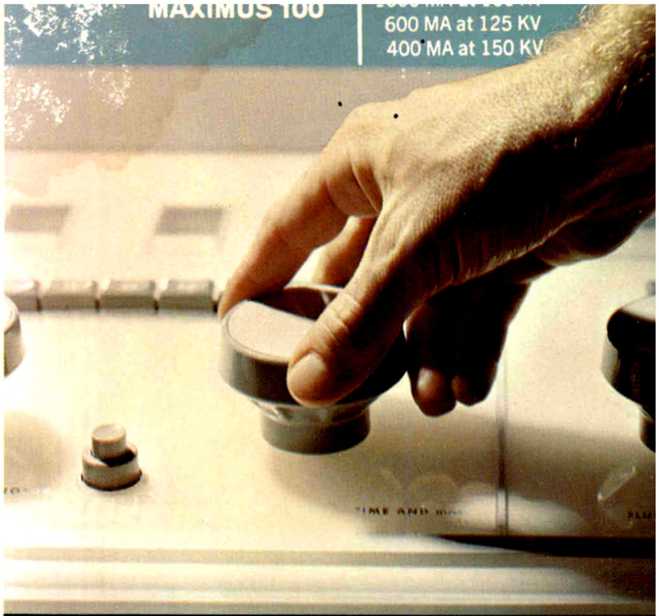
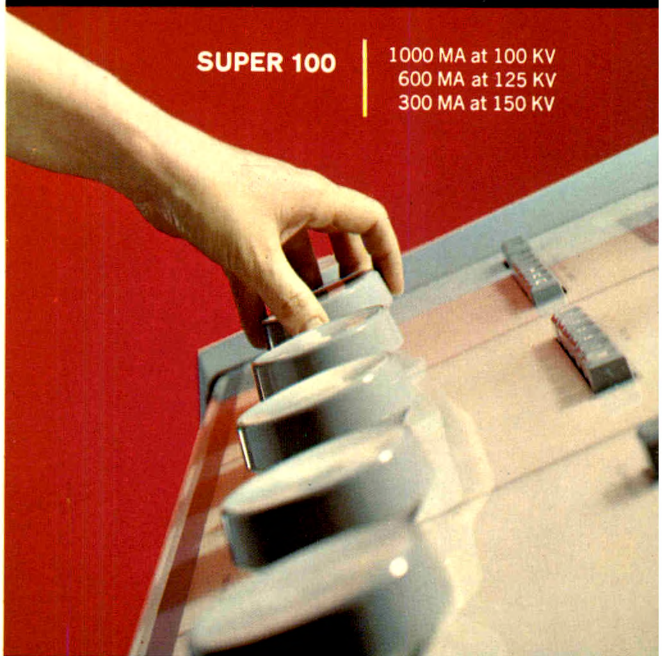


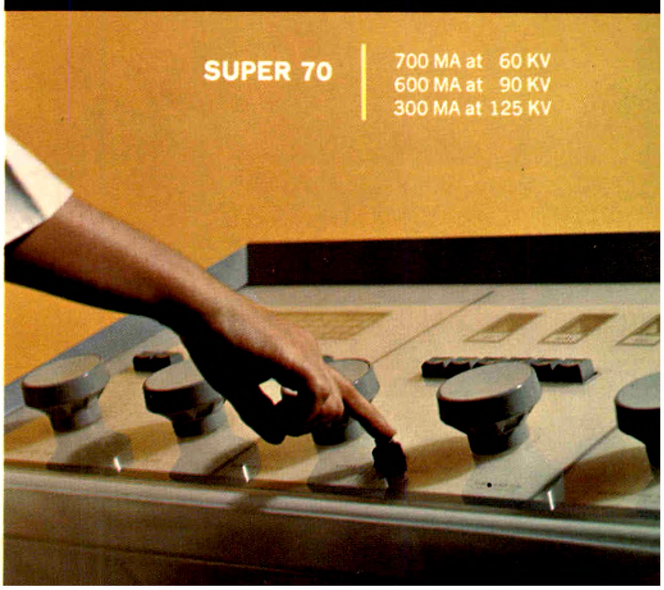


"Falling load" is a technique of tube loading especially suitable for use with phototiming. It produces radiographs of proper density regardless of patient size — without endangering the x-ray tube — in the shortest possible times.

In comparison with other tube loading systems, a Norelco generator initially loads tubes to maximum capacity. Then the load "falls" in approximate relation to the tube's loading capacity as the exposure progresses. When appropriate MAS (as measured by ionization chambers or photo pickups) is reached, the exposure is automatically terminated. This method guarantees proper radiographic density, yet utilizes the tube optimally.







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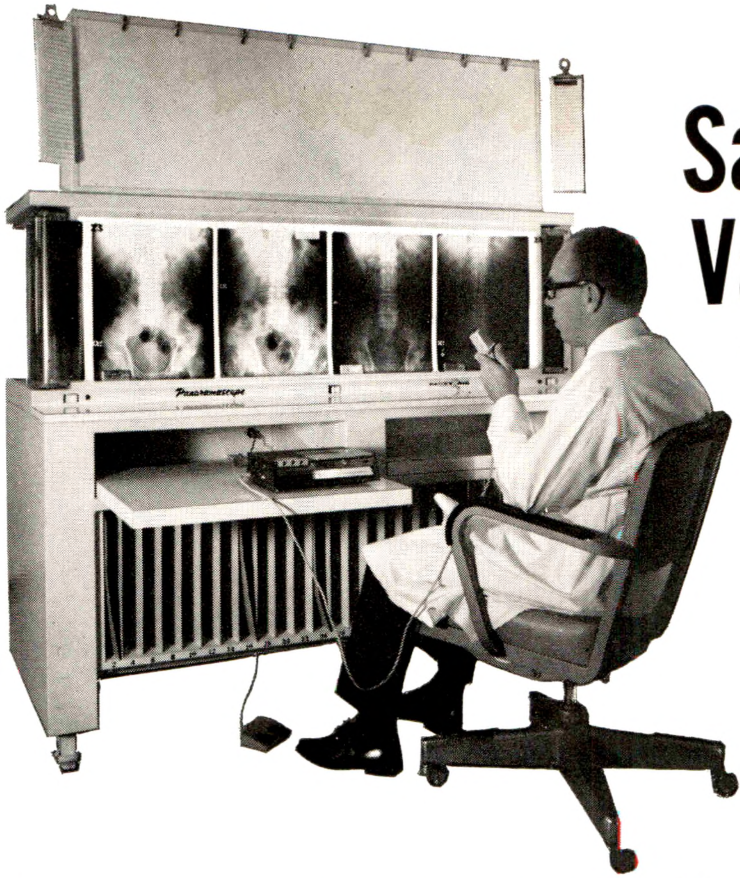
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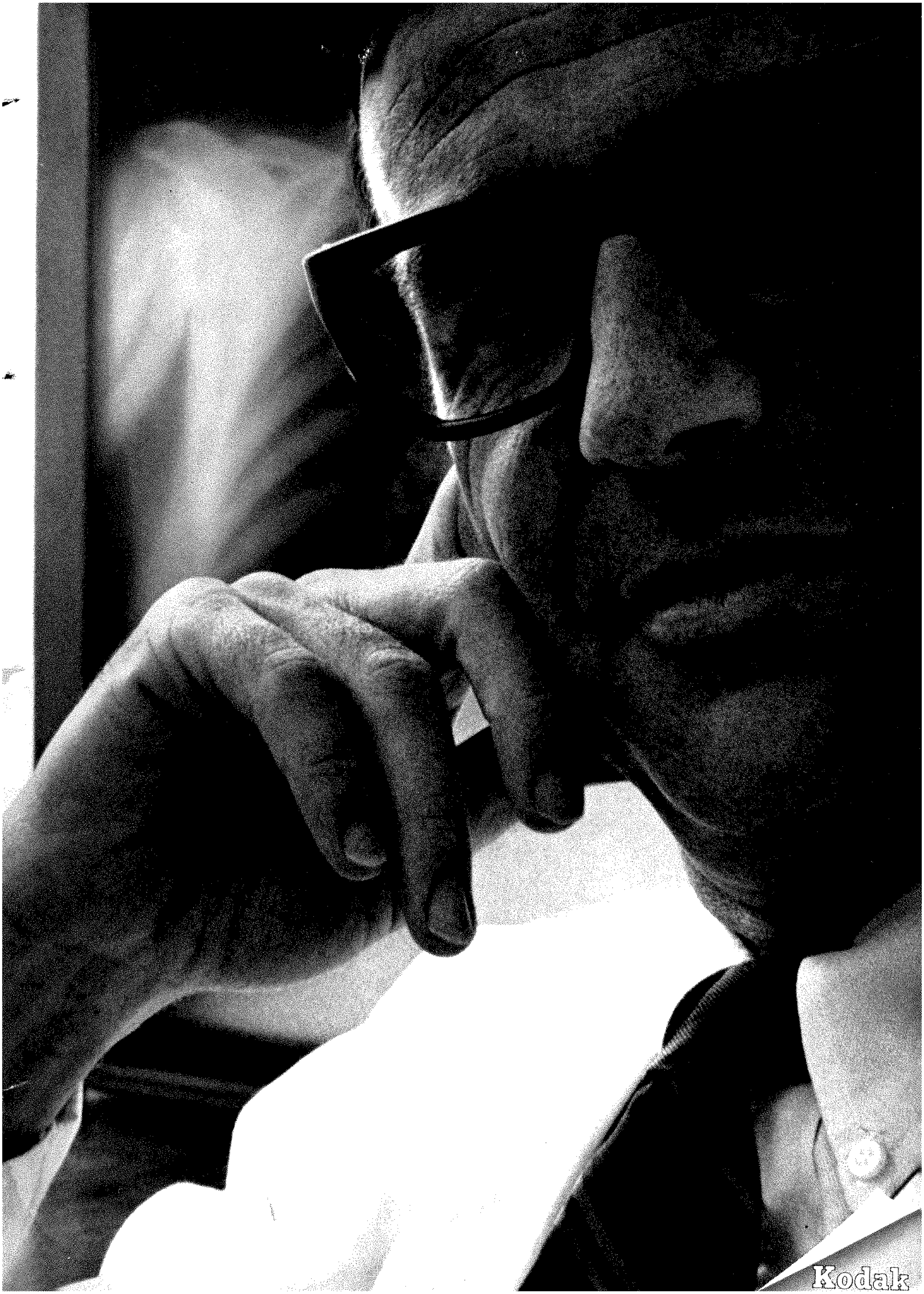
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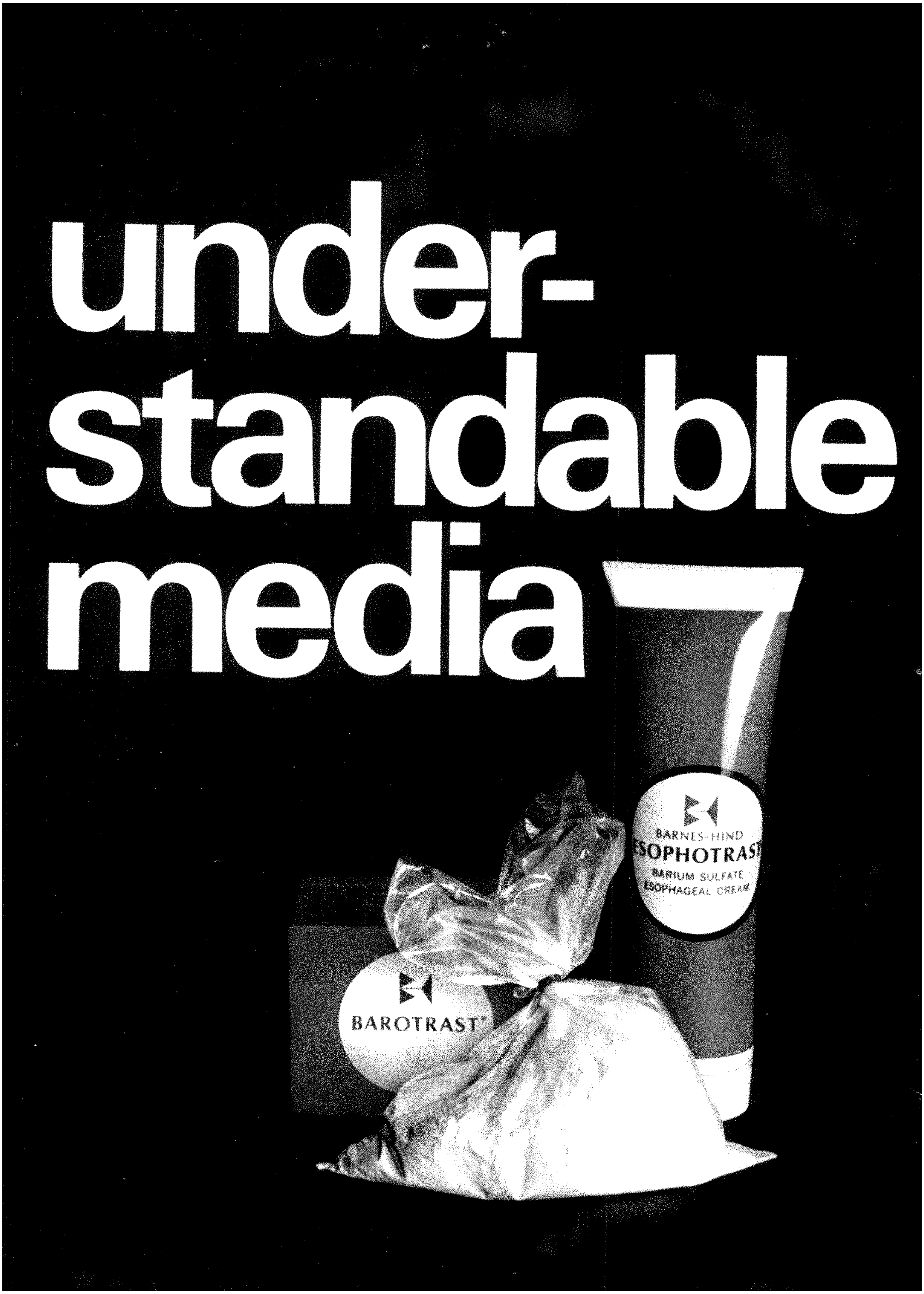

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THE AMERICAN JOURNAL
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RADIUM THERAPY AND
NUCLEAR MEDICINE

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"THE LIGHT IS BETTER HERE!"*

THE PRESIDENT'S ADDRESS, 1967

By MILTON FRIEDMAN, M.D.
NEW YORK, NEW YORK

FOR more than 40 years, I have watched the science of radiation therapy evolve by means of slow accretions of knowledge interspersed with a few major jumps. This type of evolution, as with many other branches of medicine, has been variously designated as empiric, pragmatic, technologic, or applied science. We are repeatedly told that only fundamental studies conducted in the laboratory can lead to the solution of the problem of cancer, and this may very well be true.

However as I survey the panorama of research into the laws of nature, and see that many of her truths are discovered outside the laboratory, a much neglected area which is nevertheless inhabited by many great intellects, I am reminded of an ancient story. It tells of a man on hands and knees scratching around in the dirt. A friend asked, "What are you doing?" I am looking for my key." "Where did you lose it?" the friend asked. "Up there near the house." "Then why are you looking for it down here?" "The light is better here!"

In our culture, the role of the physician-scientist is to heal sick people. Yet why have so many dedicated their lives to eradicating cancer from the society of rats and mice. Is it because "the light is better there?" Why struggle to develop a new idea or discovery by observing perverse human beings? Many never complete their treatment; they often fail to take prescribed medicine; they fail to keep appointments; the vagaries of intercurrent disease or poor general health commonly obscure the unknown factor being studied; many patients are lost to follow up. It is so much easier to work in the laboratory with complaisant rats. They follow instructions; the follow up rate is 100 per cent; controls are readily available. The experiments on rats satisfy Dirac's criteria of being neat and elegant.

Of course the laboratory animal is vital in most biologic investigations, although the researcher should extend his interests beyond the horizon of exclusive iatrogenic animal husbandry. The study of the patient and his tumor can yield valuable clues pointing toward basic laws. This is achieved in three ways. Ideas developed in the

* Presented at the Forty-ninth Annual Meeting of the American Radium Society, Toronto, Ontario, Canada, May 29–31, 1967.

laboratory must ultimately be tried on the patient. (Anachronistically, many sophisticated radiobiologic investigations have merely refined the principles employed in routine clinical practice many years after their discovery by the intuitive pioneer clinician.) The second way is exemplified by the many great discoveries made outside a laboratory: Archimedes and the bathtub, Newton and his symbolic apple, Semmelweiss and puerperal sepsis, Bequerel's radium burn, and Coutard's application of Regaud's principles, one of the great advances in radiation therapy. In the third and most common type of medical discovery, the patient is the test object. One investigating physician endowed with high intellect and intuitive creative imagination, motivated by a personal commitment toward discovery, who blends his original ideas with a broad knowledge of associated sciences, can by a series of gradual studies advance medicine a giant step. An example is Dr. Harvey Cushing's discovery of how to remove a brain tumor. This experiment lasted a lifetime. The first 25 patients died. Undaunted, Dr. Cushing continued to look for the key where the light was poor, and from his and others' efforts was developed the science of neurosurgery. Medicine is pervaded with many similar examples. This type of intellectual creativity is a basic science. The key is the *persona* of the investigator.

In research we must acknowledge the importance of certain powers of intuition, without which inventors and scientists could neither rationally select particular problems nor pursue any chosen problem successfully. Polanyi has called this *strategic intuition*. It is a value judgement derived from the accumulation of ideas and experiences in the subconscious mind. It is practiced every day: by the investigator who decides which of several potentially fruitful avenues should be explored; by the director of a research institute; and by officials charged with the responsibility for approving research grants. The scientist must be able to estimate the gap between his knowledge and abilities on the one hand, and the discovery itself. The product of a lifetime of scientific endeavor depends to a great extent on strategic intuition. Without it, a brilliant intellect bears little fruit.

I will cite two examples of the operation of strategic intuition. After working with increasingly powerful supervoltage x rays for about 10 years, it became evident to me early in the 1950s that the results of treatment were dictated more by the characteristics of the cancer rather than the type of radiation. My enthusiasm for still higher energies waned. Colleagues in other cities and other countries came to similar opinions similarly, even before their results had conclusively demonstrated the validity of this opinion. These opinions were derived not from abstract intuitions, but from scattered observations by many investigators in many cities. The important point is that although each one came to a similar conclusion which was not substantially supported by facts, the conclusion became generally accepted, and this acceptance strengthened the conclusion.

The second example of strategic intuition leads toward disunity rather than unity. For the past 35 years I have been studying the effect of the "overall-time" factor on a course of radiation therapy. After some years, my strategic intuition told me that further studies of this time factor would not be fruitful except perhaps that 3 treatments per week might be just as good as 5 treatments per week. However, there is an opposing school of thought composed of two groups: the clinical radiotherapists who believe that the time factor is important and who continue to design new investigations; and a vast number of radiobiologists who have conducted elegant studies on a broad spectrum of animals ranging from one cell to four legs and who proffer innumerable solutions to the problem, without any charge whatsoever for these valuable opinions. Although my own strategic intuition con-

tinues to tell me that the time factor is not very important, I still pursue these studies chiefly to maintain the counterpoint in this scientific dialogue. As a matter of fact a colleague will present one of these studies at this meeting. I guess that this is good science, as it is devoid of objectivity!

Objectivism denies the personal, tacit, instinctive human appraisal of hypothetical theories. But true objectivism does not exist. The beholder sees not only with the retina, but also the hindbrain and his associated experiences. He then appraises all these with the aid of his corollary knowledge and his biases. Each individual views facts differently depending upon his intellect, his creative imagination and his fundamental esthetic sense. His deductions also depend upon whether he is close to the object so that his field of vision encompasses only that object, or whether his intellectual observation platform is at a distance so that he scans a panorama and appraises the specific object in relation to the entire scene. In a slightly different sense, there is the example of the archeologist who, in flying over territory of potential interest, has been able to see the outlines of an ancient ruined city or palace, whereas on the ground he perceives nothing.

The scientist first works on intuition and then rationalizes later. He thinks he proceeds from one rational step to the next, and on occasion does so, in which event he progresses a minuscule step ahead. The great discoveries arise from the intuition taking a giant step to the top of the mountain in theoretical conception. The scientist then proceeds laboriously to ascend this height himself; or his successor does it.

All creation emerges from chaos. Current investigations into progressively smaller subatomic particles are disclosing a number of corpuscular units such as mesons, pions, lambdas, negatrons, sigmas, etc. and such phenomena as electron spin resonance, parity, etc. Thus the oversimplified atom that we delighted in 25 years ago, based on the proton, electron and neutron, is not true. The most fundamental forces are numerous, varied, and seem apparently progressively more chaotic. Chaos becomes organized into complexity. The more that science illuminates complexity, the more darkness does it see. This is the course of progress. The rad is not yet understood because the problem of absorbed dose has been oversimplified for the lack of understanding of its primordial chaotic milieu.

The scientific aptitude pursues proof of knowledge. Many alleged proofs become false with increased experimentation, and are discarded. The durable building blocks remain. A major source of trouble stems from the large group of cloudy-thinking "scientists" who draw inflated and allegedly significant conclusions not warranted by their data. As Niels Bohr said to a talkative student, "You are just being logical; you are not thinking!" This plurality of workers is not scientific but scientistic. They are the fools. We must be aware of them and their conclusions which are based on an unreasonable use of reason.

The scientist believes that he pursues truth objectively in a disciplined and objective world. This ideal of strict objectivism is unobtainable, and more than that absurd. Probably not one person here today surveyed the entire cosmos to decide which was the most important problem in which to dedicate his life, and then made a personal decision to work on cancer. Undoubtedly in every instance the decision was thrust on us by chance, coincidence, circumstances beyond our power to predict or to influence, or dynamic forces which happened to move within our personal orbit at an appropriate moment when we were ripe to select a career. Any attempt to define this first decision as objective is patently wrong.

Every scientist in creating a theory commits his essence or being, by a supreme intensification of a uniquely personal intimation, to the creation of that theory. He pursues it with the passionate urge to fulfill self-set standards. The quality of the product is related to the standard. Every

investigator is in fact making an intimate pronouncement about himself. His report often yields more information concerning himself than the subject under study.

There is a difference in the true creative genius who evolves a theory from his own essence, as contrasted against existence (nature) where things are waiting to be discovered. Each creation or discovery must be tested before a jury of fellow men, who contain the entire spectrum of mankind's essence from time immemorial. This is where bias meets counter-bias and is neutralized by the multiplicity and variety of individual biases, which tend to lead toward truth. We are all prejudiced, as man has need for prejudice in order to be distinct.

The early Greeks and Romans invented useful gods, each god representing one or several aspects of man's psyche or soma or combinations of both. Their gods were simple though profound; mixtures of strong and weak; consequently human, and consequently fallible. Yet they were efficient spiritual executives. Our contemporary civilization is far more complex and has confused us. In a paranoid-like fashion it has concocted a group of religions, each with its respective God, so far superior to any individual on this earth that it is impossible to approach Him in caliber. One god for each tribe; each functioning with a similar set of rules; rather good ones. Unfortunately in that segment of contemporary civilization which is called science, there never existed a proper Deputy God of Science. The Romans had one available. His name was Janus. He was two-faced: spiritual and demonic. If we scientists dared to be truly objective, we would adopt him as our God of Science. He has all the necessary attributes: high-minded and dedicated on the one hand, egocentric and often unscrupulous on the other; intellectually dispassionate, and occupationally passionate; a diligent researcher of the literature, and an occasional plagiarist; a strictly objective observer, especially of those facts which support his thesis. His deification is redeemed by the occasional genius, the brilliantly intuitive observer of a fleeting fact which might be the core of a major concept such as the slight differences in atomic weight which led Einstein to suspect the power potential in the atom. Parenthetically Janus was an ancient Roman deity, primarily the God of gates and doors, and hence of all beginnings; which symbolizes another necessary attribute of the successful scientist, namely the two signs commonly found on the opposite sides of a door, "push" and "pull." But the truly divine aspects of our scientific Janus lie in the eternal heritage of knowledge built by so many of his sons and martyrs.

The science of the cosmos is founded not on objective data but on a "belief." We believe that the primordial chaotic gases which preceded the formation of the Earth, somehow or other by random chance, a euphemism for God, congealed into solids, the solids into chemicals, the chemicals into living substances, and by natural selection the living substances evolved to contemporary Man, a state which is only halfway up the evolutionary ladder toward excellence. This major foundation of science is supported by shreds of objective data and an enormous component of faith or belief. Some beliefs are more readily accepted than others. I wish I could believe with certainty that a cancer cell is a genetically mutated normal cell. It would be so easy to join the cult of pure objectivism and thereby become relieved of all responsibility concerning this belief. From the fundament of beliefs are created hypotheses which are the pathways of scientific exploration.

The cliché that "the computer returns an analysis only of the data put into it" should be extended one dimension. We introduce into our cerebral as well as mechanical computers data based only on those parameters which we know; and often get wrong answers. Most problems have parameters of which we are ignorant or which may seem irrelevant. For the lack of

these data we fail to obtain true answers.

The knowledge which we bring to a problem tends to pin us down, to imprison us in what should be no more than a frontier position. We must live on the frontier of our being where the known is contained in the infinite unknown, and there should be a continual crossing and recrossing of tentative borders.

There is a rhythm to science. An era of discovery is followed by exploitation, at first dynamic and rapid, then through lesser cycles, each epochal peak of which becomes in reality a summer zephyr, soothing to the cheek or the ego of the investigator, whose sandpile of discovery is promptly washed away by the ocean of reality.

The ideal scientific dialogue is an exchange of ideas among individuals in the vanguard of their field. A large number of dialogues occurring simultaneously throughout the World provide the intellectual soil from which a few geniuses may derive nourishment and may advance knowledge a giant step. We need a flow of their new ideas into the reservoir of basic concepts concerning cancer.

Therefore let us begin today's dialogue between the speakers who will appear on this rostrum and the audience of their peers.

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HYPERBARIC OXYGEN IN RADIATION THERAPY*

AN INVESTIGATION OF DOSE-EFFECT RELATIONSHIPS IN TUMOR RESPONSE AND TISSUE DAMAGE

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MUCH experimental and clinical effort has been expended in attempting to differentially sensitize tissues to ionizing radiations, and increasing the so-called "therapeutic ratio" in radiation therapy. In general these attempts have not produced dramatic results. Many substances which appear to act as true sensitizers *in vitro* or as agents with additive toxic effects have been tried. The only substance with proven capacity to modify radiosensitivity at a cellular and tissue level and be essentially devoid of additive toxic action to cells is molecular oxygen. This property—the so-called "oxygen effect"—has general applications in tumor radiotherapy. The quantitative characteristics of the relationship between the biologic effectiveness of radiation dosage and the partial pressures of oxygen in tissues appear unique and of great therapeutic potential if one accepts the view that cellular radioresistance of solid tumors in man is due to the presence of tumor cells which are anoxic but viable.

It is not my proposal to introduce an historic account of the "oxygen effect" in radiotherapeutics. This dates back to the beginning of the century and has been ably reviewed by Churchill-Davidson.[5] However, I must enumerate a few milestones crucial to its development and application to radiotherapy, namely, the pioneering studies of the late L. H. Gray and his colleagues,[10,17,48] the studies of Alper and Howard-Flanders[1] which provided a quantitative relationship between cellular radiosensitivity and partial pressures of oxygen, the *in vivo* assay studies with murine tumor cells[18,36] and the pioneering studies of Churchill-Davidson and his colleagues with high pressure oxygen in radiotherapeutics[3] and also in being first to use the tourniquet-hypoxia technique in radiotherapy of limb tumors.[3] Many other individuals and centers have made important contributions directly and indirectly related to the problem. Particularly important are those studies specially directed towards determining the effects of oxygen tensions in excess of ambient levels in enhancing the radiosensitivity of normal animal tissues such as growing bone,[20] skin and connective tissues,[49,55,65,66] lung,[30,56] kidney,[9] the neuraxis[67] and the whole body;[39,51] also, quantitative determinations of oxygen effect in human tissues, such as those of Suit[44] and others[54] are of even greater interest to the radiation therapist, but at present we would welcome much further information in this respect. However, we are still somewhat ignorant of equally fundamental biologic problems relevant to the design and prescription of the most effective radiotherapy, and which continue to provide scope for much argument and disagreement—both in the realms of "hybaroxic radiotherapy" (what a dreadful expression!) and what is usually termed conventional radiotherapy. I refer particularly to fractionation of dose and the spacing of fractions in respect to biologic equivalence of dose effect in tumors and normal tissues. At present, conventional daily fractionated radiotherapy remains in favor and the short term large fraction techniques employed by most

* The 1967 Gordon Richards Memorial Lecture, delivered in Toronto, Ontario, Canada, under the auspices of the American Radium Society at its Forty-ninth Annual Meeting, May 29–31, 1967, and based on the author's clinical and experimental studies at the Cancer Institute, Melbourne, Australia.

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centers using HPO, do not enhance its popularity. Indeed even the radiobiologists appear to have been urged to prove that conventional daily fractionated radiotherapy incorporates fundamental biologic principles which allows one to question or ignore tissue anoxia to be a theoretic obstacle to successful treatment, or in themselves provide conditions which adequately reverse radiobiologic anoxia of tumors. However, evidence is accruing that long term daily fractionation may not be as completely efficacious as thought and that good results are achieved by other schedules.[8,16,40,42] Such modifications in fractionation have been encouraged by a more accurate quantitative knowledge of radiation lethality at a cellular level—knowledge one can attribute to the metamorphosis brought about in mammalian radiation biology by the techniques of Puck and his colleagues.[36,37] These have provided more accurate and critical concepts of the parameters of radiosensitivity of normal and malignant cells[36] and set the scene for a more sophisticated appreciation of the effects of fractionation of dose as a result of the *in vitro* split-dose studies pioneered by Elkind and Sutton[11] and others. Needless to say, vexing deficiencies still exist in our present radiobiologic knowledge and ability to formulate fractionation-dose schedules with sufficient confidence to be generally applicable to radiotherapy. Nevertheless it seems desirable for the radiotherapist to adopt a radiobiologic approach to unsolved practical problems, if this appears at all feasible in the light of existing experimental data and theory. Since 1961, in Melbourne, a clinical project to study the effects of hyperbaric oxygen (HPO) in radiotherapy has been conducted with this aim very much to the fore, and the principles of cell survival theory have been used to analyze results and to introduce new dose schedules, particularly in respect to fractionation. I propose to present some results of treatment for advanced neoplastic disease of the upper digestive and respiratory passages and the bladder respectively, and discuss the effects of fractionation for the rather limited range we have used in these studies.

HPO—IRRADIATION PROTOCOL—DOSAGE

A summary of case selection, treatment policy, incidence of hyperbaric oxygen toxicity and dosages used is shown in Tables I–IV. The technique has proved safe and was rapidly introduced as an almost routine departmental discipline. It is well within the scope of a moderately sized radiotherapy department provided with suitable megavoltage equipment and access to beds for patient care. The techniques we use are very well tolerated by patients. No patient refused treatment and only 1 patient in our series to date was unprepared to continue. The incidence of radiation sickness has been remarkably low and usually absent, and an unexplained sense of well-being is often expressed by patients undergoing a course of treatment. Bilateral myringotomies performed before each HPO exposure cause few problems or after effects, and patients usually leave the hospital between successive treatments given under anesthesia. This project has been pursued with a view to deciding certain major issues:

(1) To determine regression rate and absence of clinical regrowth of advanced malignancies of poor prognosis. Advanced tumors of the upper digestive and respiratory passages and bladder have provided the bulk of material referred for treatment.

(2) To determine regression rates for a limited range of fractionated doses (Table IV) and to correlate these results with survival of patients and complications attributable to irradiation of normal tissues with lack of tolerance.

(3) To attempt an analysis of such dose-effect data in terms of cell survival theory and radiation lethality at a cellular level based on the "multihit" type cell survival curves obtained for oxygenated cells and tissues.

I have taken the view that unless such data are available and a valid methodology

TABLE I

CASE MATERIAL

Histologically proven disease Stages $T_{3,4}$, $N_{2,3}$ or III, IV
~20–40% cases recurrent following previous surgery in various sites
No upper age limit in selection (21% cases over 70 years)
Cases with distant metastases other than in regional lymph nodes included
(~10% in head and neck cancers ~15% in bladder cancers)
Treatment refused on medical grounds (~1%)

established for the analysis of dose-effect in fractionated radiotherapy in HPO, an introduction of clinical trials to evaluate a HPO technique, or for that matter a related nonhyperbaric technique, is undesirable, illogical and hardly ethical, and would not pass critical examination. Only recently, have sufficient HPO dose-effect data become available to us, to tentatively commence clinical trials. I will refer to these later.

Naturally it is somewhat presumptuous to employ cell survival curves and parameters, essentially based on *in vitro* studies, to design a clinical experiment and analyze the results obtained. Our attempts to do so must be taken in proper perspective. However, certain radiotherapeutic principles which enjoy general acceptance can be supported also on radiobiologic grounds and suggest that there is in fact a radiobiologic explanation for sound clinical methods.

Both radiotherapist and radiobiologist generally agree that higher cumulative doses of x rays are tolerated by cells and tissues if the number of fractions given is increased. Attempts have been made to formulate such divided dose effects quantitatively for conventional fractionated

TABLE II

TREATMENT POLICY

4 Mev. x irradiation in 45 pounds per square inch (psi) 4 atmospheres absolute (ATA) O_2 under general anesthesia with intubation
Large field "regional" irradiation techniques including ipsilateral and contralateral lymph nodes with shielding out of "vital" tissues if possible
2–6 fractions spaced over period averaging 21 days (7–28 days)
All fields treated at each hyperbaric oxygen (HPO) session

TABLE III

OXYGEN TOXICITY

3,200 HPO EXPOSURES UNDER ANESTHESIA IN 780 PATIENTS WITH ADVANCED MALIGNANT DISEASE (1961–1966)

Average duration of each exposure at 4 ATA*	44 minutes (range 27–65 minutes)
Convulsions	10 (0.3%)
Other toxicity to neuraxis	nil
Lung damage	nil
Other tissues	nil
Mortality	2† (0.3%)

* Includes decompression time (6 minutes).
† Both due to postanesthetic respiratory obstruction and not to oxygen toxicity.

TABLE IV

DOSE-FRACTIONATION AND ISO-EFFECT CALCULATION IN HPO

From multihit formula for cell lethality

$$n/n_0 = [1-(1-e^{-D/D_0})^m]^N$$

or

$$n/n_0 \simeq [me^{-D/D_0}]^N$$

($D_0 = 130$ rads
$m = 2$
N = number of fractions, each D rads)

Dosage (rads)	Spacing	n/n_0
2×1,000	0, 7 days	5×10^{-6}
3×1,000	0, 7, 21 days	10^{-8}
3× 800	0, 7, 21 days	5×10^{-7}
6× 500	0–17 days	10^{-7}
6× 600	0–17 days	10^{-9}
4× 725	0–21 days	5×10^{-8}

treatments, *e.g.* in terms of the log—log plots of dose and over-all time of Strandqvist[43] or the modification suggested by Ellis,[12] and Fowler and Stern[14] to use number of fractions to replace time. However, a straight line as in the Strandqvist relationship does not fit certain experimental data for 1–10 fractions.[46] The more formal analysis used in our own study is summarized in Table IV. A multihit equation is used to translate a fractionated physical dosage into a corresponding biologic effect. This of course involves an arbitrary selection of certain parameters—the slope constant D_0 and the extrapolation value m. It has been assumed that the tumor (and tissue) is fully oxygenated in respect to radiosensitivity and a value $D_0 = 130$ rads has been chosen as a reasonable approximation for normal and tumor cells under oxygenated conditions in tissues. Available experimental data have made the choice of an extrapolation number more difficult in attempting to fit data and to calculate isoeffect dosages. While most *in vitro* studies have given values of m in the range of 2–6, *in vivo* studies still present a confused picture and very high values have been reported for certain animal tissues. However, recent experimental work[59] suggests that "regenerative" factors in complex tissue systems, closely associated with cell repopulation of an irradiated tissue, have complicated the interpretation of some *in vivo* results, in which the "sparing" effect of fractionation is predominantly attributed to recovery of sublethal damage to radiosensitive targets at a subcellular (molecular) level. The progressive accumulation of HPO clinical data using 2–6 radiation fractions suggests to us that a value of $m=4$ we chose originally is too high and a value of $m=2$ appears to provide a better fit for the data obtained.

CANCER OF THE UPPER DIGESTIVE AND RESPIRATORY PASSAGES

The objective end points adopted in the Melbourne project to assess results have been:

(1) Clearance and persisting regression of primary growths and their lymph node metastases after irradiation.

(2) Cumulative survival rate of patients.

(3) Incidence of severe radiation induced complications (necrosis, myelitis, etc.)[53,57]

Data for clearance rates of 268 T_3 T_4 primary tumors and 208 N_2 N_3 lymph node metastases in 297 patients are summarized in Table V and in Figure 1; n/n_0 values ($D_0 = 130$ rads, $m=2$) corresponding to the fractionated treatments ($N \times D$) have been used to plot dose-effect data. In this analysis those patients showing recurrence following previous irradiation have been excluded; also those in a moribund state before treatment in HPO and who died within 3 months have been excluded, irrespective of whether good clinical resolution occurred or not, since the assessment of radiation effects in these cases was most dubious. Inclusion of these cases would decrease cumulative survival rates by approximately 5 per cent.

Although there is some scatter of points, a line can be fitted to these data and shows a definite trend over a dose range equivalent to $n/n_0 = 10^{-5}$–10^{-9}. Clearance rate increases at an essentially linear rate over the range 10^{-5}–10^{-7} but beyond 10^{-7} the clearance rate flattens out at a 70–80 per cent level. *Thus by continuing to increase the effectiveness of the dose used beyond a certain value, no more cancers are cleared in HPO.*

To explain this phenomenon, certain factors may be involved:

(1) Twenty to thirty per cent of tumors were too large and contained too many viable cells to sterilize with irradiation, even if all cells were radiobiologically oxygenated.

(2) The poor response of a number of tumors was due to a radioresistance caused by some factor other than anoxia.

(3) Assessment of clearance rate is at fault.

(4) The method used to plot dosage in terms of cell survival is not valid.

(5) The HPO technique failed to ade-

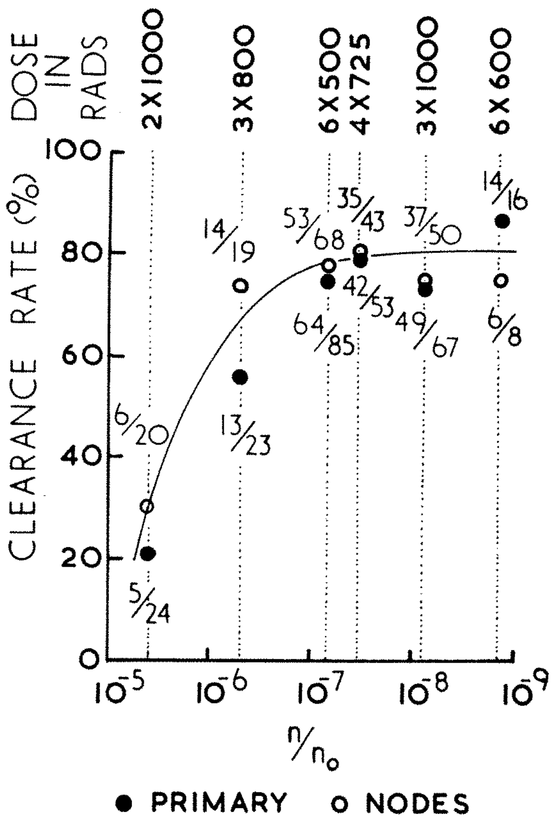

FIG. 1. Dose-response curve for advanced primary tumors of upper digestive and respiratory passages and lymph node metastases treated in hyperbaric oxygen (HPO) with 4 mev. x rays (n/n_0 values based on $D_o = 130$ rads, extrapolation number $m = 2$).

quately oxygenate 20–30 per cent of tumors.

(1) While tumor size must be a factor, since a doubling of tumor diameter could increase the number of viable cells by almost one logarithmic power, if all other factors are equal, this explanation seems not altogether satisfactory since:

(a) an increase in dose corresponding to a decrease in n/n_0 from 10^{-7} to 10^{-9} (2 log values) did not increase clearance rates; and

(b) a close correlation was not observed between size of tumor and the clearance rate in HPO although most recurrences were amongst large T_4 tumors with deep seated invasion of bone and avascular connective tissues.

(2) Radioresistance due to factors other than anoxia is plausible. However, response could not be correlated with Grade of tumor or other histopathologic features. Also, in a series of 13 cases of inoperable, recurrent or advanced melanoma receiving doses in HPO equivalent to $n/n_0 < 10^{-7}$, the regression rate was good and maintained in 9 cases (69 per cent), with 5 cases surviving at 20–43 months after irradiation.

(3) It is possible that tumor recurrence may have been confounded with adjacent tissue necrosis produced by higher doses (*e.g.* 3×1,000 rads) and an associated decrease in survival of such patients (to be discussed) could also have caused a wrong assessment. However, autopsy and biopsy studies, admittedly subject to error as shown by Suit and Gallager,[45] appeared to confirm recurrences suspected on a clinical basis.

(4) Even if one does not accept this method of analysis other time-dose plots would lead to a similar conclusion, that increase in dose beyond a certain level did not increase clearance rates.

(5) That HPO did not reverse tumor anoxia in 20–30 per cent of tumors would seem to adequately explain the findings. This is supported by our previous finding that similar large doses (3×1,000 rads) administered in air in similar case material yielded clearance rates of less than 30 per cent, *i.e.*, less than half those obtained under hyperbaric conditions.[53,57,58] Indirect support for this view is also provided by electrode measurements of pO_2 in human tumors under HPO.[22] There seems little doubt that tumor size is related to tumor anoxia, and higher clearance rates of 80–90 per cent or more are obtainable in most centers with early head and neck disease treated radically in air. Thus in a personal series of 129 cases of proven skin and eyelid cancer given 3×1,000 rads superficial x ray therapy in 2–3 weeks, 117 cases were fol-

lowed up for 2–6 years after irradiation and only 2 tumors recurred (<2 per cent) and radiation necrosis occurred in a further 2 cases. Such results with early and smaller cancers treated with x rays along conventional lines, must be taken into account, not only in rationalizing the use of HPO in early disease, but also in evaluating tumor oxygenation in spontaneous human tumors and the relative radioresistance *in vivo* reported for most solid transplantable animal tumors, no larger in size. In the latter, radiosensitivity and cure rate can be increased by HPO[17,52] but with increase in size of such experimental tumors the cure rate rapidly diminishes even if HPO is used to correct anoxia,[17] *i.e.*, sufficient increase in size and the type of tumor stroma derived from certain normal tissues[26] are undoubtedly associated with tumor anoxia, difficult to reverse.

If the tumor clearance rate data obtained in head and neck tumors in HPO and shown in Figure 1 are now contrasted with survival and necrosis rate in the same patients interesting therapeutic facts emerge (Fig. 2). Thus survival at 1 year rises steeply to approximately 65 per cent at a dose equivalent of $n/n_0 \simeq 10^{-7}$ but with further increase of dose, falls despite a constant high clearance rate. This *fall in survival coincides with a sharp rise in radiation necrosis and morbidity* from approximately 15 per cent at $n/n_0 = 10^{-7}$ to 50 per cent at $n/n_0 = 10^{-8}$. Thus a fractionated dose level in HPO equivalent to a cell killing effect of $n/n_0 \simeq 10^{-7}$ provided an optimum therapeutic ratio in HPO. I doubt if modifications of fractionation using existing hyperbaric techniques will greatly change this situation. It is of interest that our own study has confirmed to a very large extent the work of Churchill-Davidson,[6] who also observed a high rate of necrosis with 3×1,000 rads and 6×750 rads maximum tissue doses (Co^{60} γ rays) in HPO, but a marked reduction in necrosis without significantly reducing clearance rates when 6×600 rads maximum tissue dose was used. Clearance rates of primary tumors and lymph node metastases in HPO reported by Churchill-Davidson using 6×583 rads maximum tissue dose in 3 weeks were 83 per cent (primary tumor) and 85 per cent (lymph nodes). This parallels our own clearance rates using 6×500 rads modal tissue dose, 4 mev. x rays in HPO in 3 weeks, *viz.* 75 per cent (primary tumor) and 78 per cent (lymph nodes) (Table v).

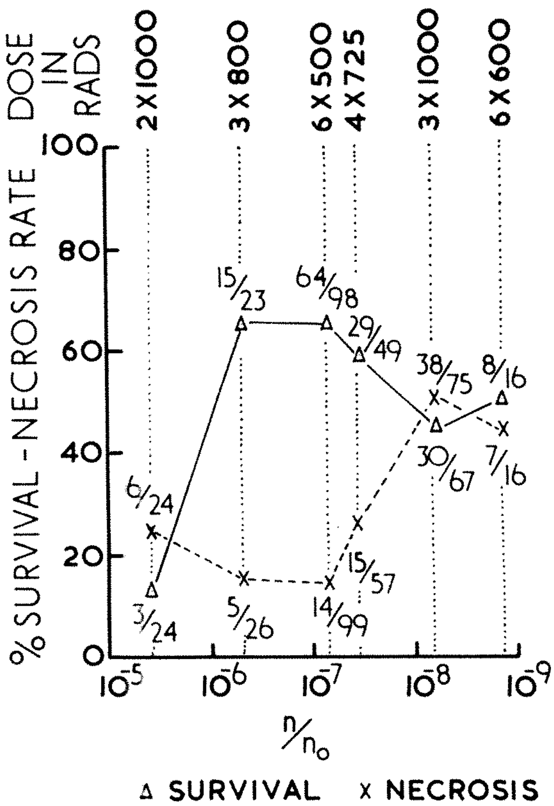

Fig. 2. Cumulative survival at 12 months and incidence of necrosis related to dosage corresponding to patients with tumors treated in HPO shown in Figure 1.

Results of treatment in HPO with 4×725 rads and 6×500 rads modal tissue doses in 156 cases of head and neck cancer may be compared in Table v. Examples of typical cases before and after irradiation are shown in Figure 3, *A–H*. Over-all clearance and survival rates and incidence of necrosis were no different for the two

Table V

RESULTS OF TREATMENT OF 297 CASES OF ADVANCED NEOPLASTIC DISEASE (T_3 T_4 N_2 N_3) OF UPPER DIGESTIVE AND RESPIRATORY PASSAGES USING 4 MEV. X RAYS WITH HIGH PRESSURE OXYGEN AT 4 ATA

	Dose (rads)						
	2×1,000 (0, 7 days)	3×800 (0, 7, 21 days)	3×1,000 (0, 7, 21 or 0, 14, 28 days)	4×725 (0, 7, 14, 21 days)	6×500 (0–17 days)	6×600 (0–17 days)	Total
Number of Cases	24	26	75	57	99	16	297
Clearance of T_3T_4 Primary Tumor	5/24 (21%)	13/23 (56%)	49/67 (73%)	42/53 (79%)	64/85 (75%)	14/16 (87%)	187/268 (70%)
Clearance of N_2 N_3 Lymph Nodes	6/20 (30%)	14/19 (74%)	37/50 (74%)	35/43 (81%)	53/68 (78%)	6/8 (75%)	151/208 (72%)
Clearance of N_0 N_1 N_2 N_3 Lymph Nodes	9/24 (37%)	20/26 (77%)	61/75 (81%)	48/57 (86%)	84/99 (85%)	14/16 (87%)	236/297 (80%)
Radionecrosis	6/24 (25%)	5/26 (15%)	38/75 (51%)	15/57 (26%)	14/99 (14%)	7/16 (44%)	85/297 (29%)
1 Year Cumulative Survival	3/24 (12%)	15/23 (65%)	30/67 (45%)	29/49 (59%)	64/98 (65%)	8/16 (50%)	149/277 (54%)

schedules. This iso-effectiveness is tendered to support the view that the lower extrapolation number ($m=2$) should be chosen to analyze dose-effect data for fractionated therapy in HPO. Thus for $m=4$, the corresponding n/n_0 values would be

$$4 \times 725 \text{ rads} \qquad n/n_0 \simeq 5 \times 10^{-7}$$

$$6 \times 500 \text{ rads} \qquad n/n_0 \simeq 4 \times 10^{-6}$$

and the effect of 6×500 rads should be similar to that of 3×800 rads ($n/n_0 \simeq 4 \times 10^{-6}$), but this has not been the case and a value $m=2$ appears to fit the entire data better.

DOSIMETRY

It is also important to emphasize that in any radiation treatment dosage errors may arise due to a variety of factors including machine output, nonuniformity of dosage in field planning etc. In terms of cell survival such errors may be of considerable importance. Thus a 10 per cent fall off in dose in an oxygenated tumor, treated with radical intent, is almost equivalent to increasing the surviving fraction of cells by one log. value. As shown in Figure 1, this could account for as much as a 25 per cent reduction in tumor clearance rate. In Figure 4 the effect of fall off in tissue dose for fractionated therapy on cell survival is shown for an oxygenated and partially anoxic tissue, respectively. It is seen that the reduction in biologic effect is even greater for highly fractionated treatments in oxygenated systems. It follows that in HPO more highly fractionated treatment does not compensate for lack of uniformity in dose distribution, and dosimetry requires the same care as in conventional treatment. In our experience with advanced disease a "marginal" recurrence due to dose fall off has not been infrequent (Fig. 5, *A* and *B*). In trying to correct these problems, considerable ingenuity in devising field arrangements is required to spare vital structures such as the neuraxis, and full rotation of the source and compensated filters should help in this respect.

CLINICAL TRIAL (UPPER DIGESTIVE AND RESPIRATORY PASSAGES)

Before proceeding with randomized trials, a pilot study was undertaken in 8 patients. These were treated conscious, breathing air at 1 atmosphere absolute (ATA) in the pressure vessel, but otherwise planning and other techniques were those used in HPO. However, dosage was increased to either 4×800 rads or 6×650 rads modal tumor dose. This 25 per cent loading of fractions was based on the assumption that HPO caused a considerable increase in radiosensitivity of all normal tissues with respect to air, in accordance with single dose Sr^{90} β radiation effects reported by us in skin.[54] The results, recorded in Table VI, showed that these doses in air

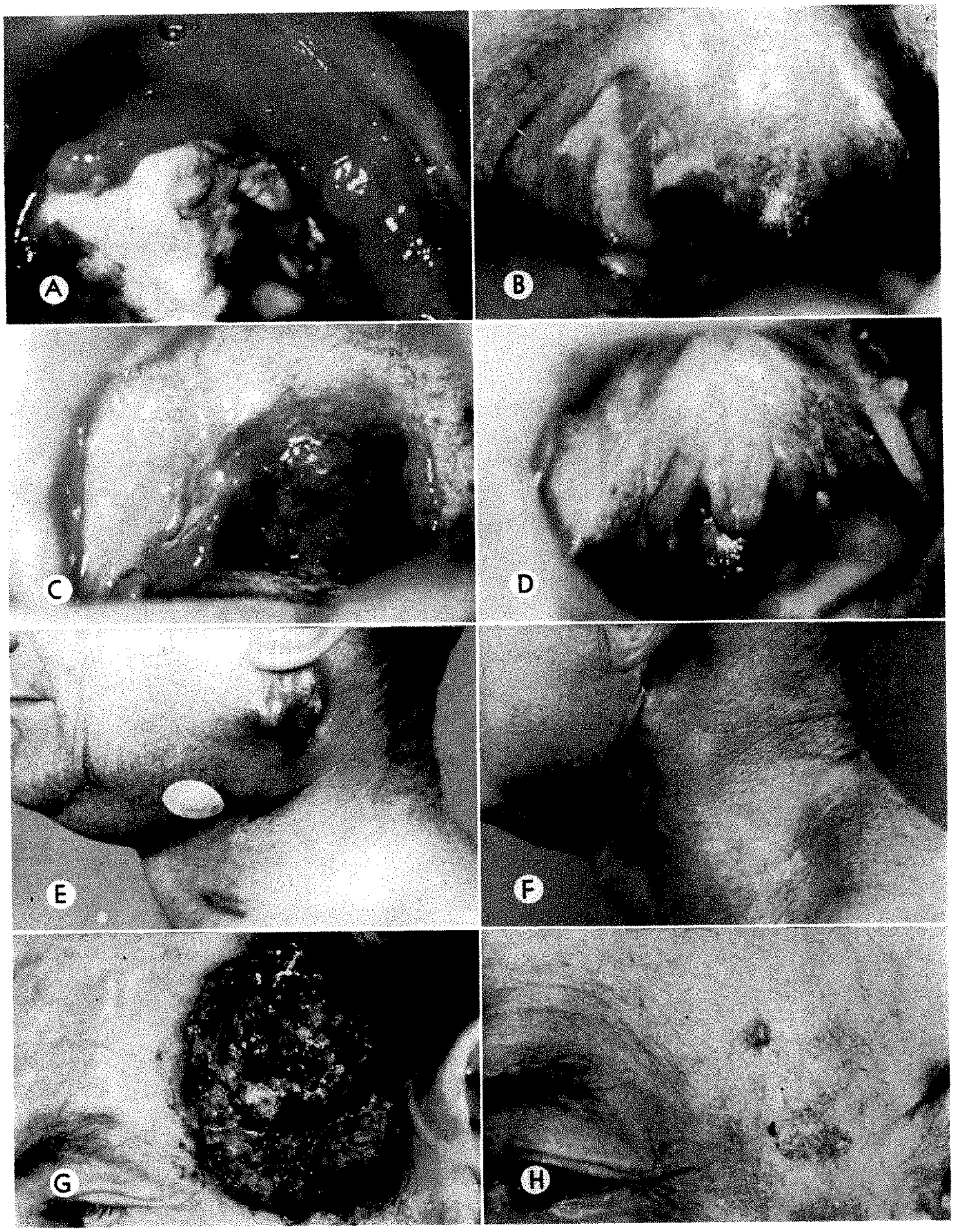

Fig. 3. Examples of head and neck cancers before and after treatment. (*A* and *B*) $T_3 N_3$ carcinoma of palatine arch (dose $3\times 1,000$ rads). (*C* and *D*) $T_3 N_3$ carcinoma of tonsil (dose 6×500 rads). (*E* and *F*) $T_3 N_3$ carcinoma of parotid gland (dose 6×500 rads with skin build up). (*G* and *H*) Carcinoma of skin (6×500 rads with skin build up).

were not tolerated by mucous membranes. In all 6 cases with prescribed 6×650 rads, the course could not be completed, and very severe reactions also occurred in the 2 cases receiving 4×800 rads. This observation made us reduce the air loading to 50 rads per fraction in two trials of HPO *vs.* Air, and the dosages used were

4×725 rads (HPO) *vs.* 4×775 rads (Air)—*head and neck trial*

or

6×500 rads (HPO) *vs.* 6×550 rads (Air)—*bladder trial*

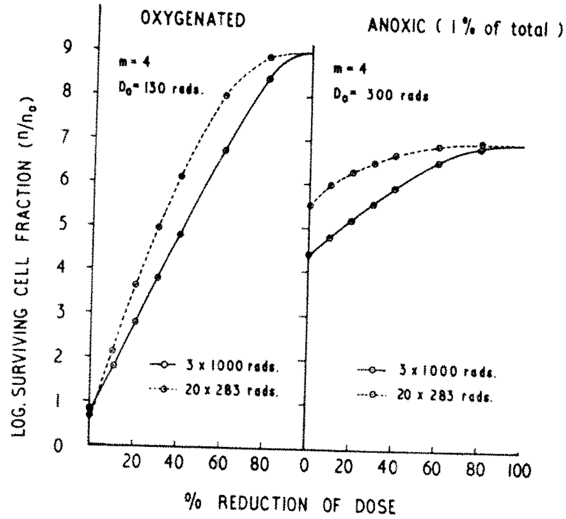

Fig. 4. Calculated effect of reduction of dose on cell surviving fraction in oxygenated and partially anoxic tumor, for courses of 3 or 20 fractions.

to provide treatments which should result in comparable tissue damage and reactions and be acceptable in respect to morbidity.

The patients in both trials were allocated to HPO or Air treatment groups according to odd or even birthday, after being first selected as suitable to enter trials on clinical grounds. Cases were not accepted if recurrence developed after previous irradiation, if blood borne spread was demonstrated or if the prognosis was considered too poor on other grounds to preclude a sufficiently long follow up for assessing tumor response. In general, HPO cases were bedded in hospital on and off during the 3 weeks of treatment involving anesthesia while most air patients were treated as out-patients.

In the HPO and Air groups comprising the head and neck trial acute mucosal and other reactions were comparable. Twenty-nine cases were allocated to this trial, which was continued for a 12 month period commencing early 1966 and then terminated. The status of 12 (Air) and 17 (HPO) patients in January 1967 is shown in Table VII. Regression in the HPO group was better and the trial was terminated, not because of an apparent statistical difference favoring HPO in this respect, but because Air treated patients fared worse in other ways. This included failure to

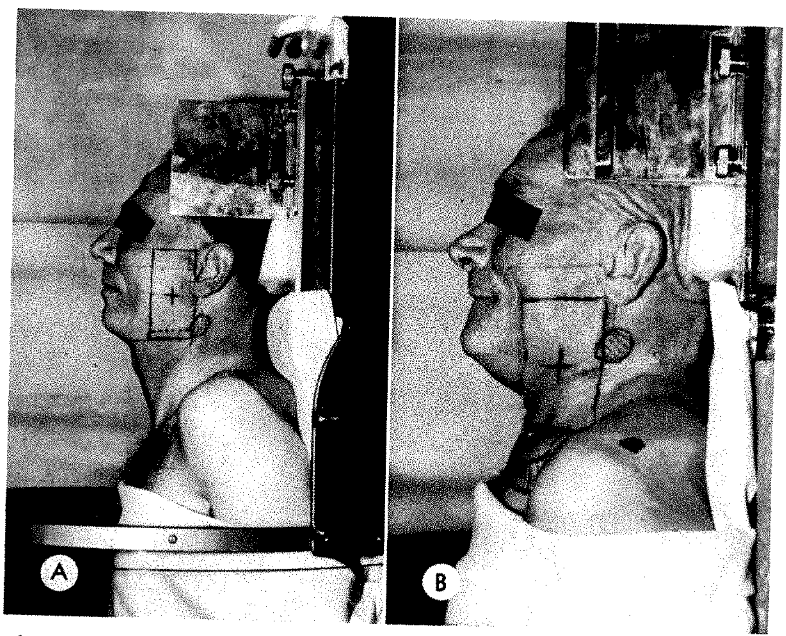

Fig. 5. Lymph node metastasis in neck (shown on skin) due to underdosage at posterior margin of opposing fields, also marked on patients (*A*) with T_3N_2 carcinoma of palatine arch and (*B*) with T_4N_2 tumor of oro-pharynx, irradiated with 6×500 rads in HPO. Re-mock up of patients in treatment position in simulator.

TABLE VI

PILOT TRIAL WITH 4 OR 6 LARGE FRACTIONS "IN AIR" AT 1 ATA WITH 4 MEV. X RAYS

Case and Stage	Prescribed Tumor Dose (rads)	Reactions	Tumor Response (Primary Tumor/Lymph Nodes)	Survival
1. Tonsil T_3 N_3	4×800 (22 days)	Moderately severe	Regression but P and N recurred within 3 months	Died 6 months—hemorrhage from primary recurrence
2. Tongue T_4 N_3	4×800 (22 days)	Severe→necrosis	P and N never regressed but progressively grew	Died 6 months—recurrence, necrosis, metastases at 4 months
3. Floor of Mouth T_4 N_1	6×650 (17 days)	Very severe and only 5×650 rads given	P and N marked regression but residue at death	Died 2 months—necrosis and metastases of lungs and abdomen
4. Posterior Pharyngeal Wall T_2 N_0	6×650 (17 days)	Very severe and only 5×650 rads given	P and N recurred within 3 months	Died 8 months—recurrence and metastases
5. Lower Alveolus T_4 N_3	6×650 (17 days)	Very severe and only 5×650 rads given	P and N never regressed—recurrence and necrosis	Died 3 months—recurrence and necrosis; metastases to liver
6. Lower Alveolus T_2 N_0	6×650 (17 days)	Very severe and only 5×650 rads given	P and N recurred with necrosis	Died 12 months—from recurrence and necrosis
7. Ear Melanoma (excised) T_1 N_1	6×650 (17 days)	Very severe and only 5×650 rads given	Clearance of lymph nodes	Died 12 months—metastases to lungs, bones, etc. at 3 months
8. Rectum (inoperable) Stage III	6×650 (17 days)	Very severe and only 5×650 rads given	Temporary regression followed by recurrence and necrosis (recto-vesical fistula)	Alive 9 months—with gross recurrence, necrosis and colostomy

check tumor growth during treatment, early rapid regrowth of tumors after a short lived regression following treatment and the higher proportion of Air patients requiring early retreatment of recurrences by radical surgery, interstitial implantation and re-irradiation in HPO in attempts to palliate. In this trial, clearance rates obtained for HPO and Air treatments respectively were very similar to those reported previously in a retrospective analysis.[57] This over-all experience, taken in conjunction with that reported from other centers in various countries engaged in HPO studies,[7,24,34,64] has encouraged us to pursue studies aimed at improving radiotherapeutic results with HPO rather than continue a time-consuming trial along present lines.

CANCER OF THE BLADDER

Our early experience of treating advanced T_3 T_4 bladder cancer with 3×1,000 rads in HPO gave unsatisfactory results[27,53,57] in that the rate of necrosis was high and largely responsible for a poor sur-

TABLE VII

"AIR VS. HPO" TRIAL* IN ADVANCED CANCER† OF UPPER DIGESTIVE AND RESPIRATORY PASSAGES

	Primary Tumor Clear	Lymph Nodes Clear	Both Clear	Survival Beyond 6 Months
AIR	6/12 (50%)	2/12 (17%)	2/13 (15%)	7/11 (64%)
HPO	14/17 (82)%	9/13 (69%)	12/17 (71%)	12/15 (80%)
	n.s.	$\chi^2=3.3$ $p>0.05$	$\chi^2=4.6$ $p<0.05$	n.s.

* Dosage 4×725 rads (HPO), 4×775 rads (Air).
† T_3, T_4, N_2, N_3 disease.

TABLE VIII

43 CASES OF BLADDER CANCER TREATED IN HPO

	Dose		Significance
	$3\times1{,}000$ rads	6×500 rads	
Number of cases	16	27	
Stage*	6 T_3 10 T_4	1 T_2 6 T_3 20 T_4	
Distant metastases before irradiation	2/16 (12%)	6/27 (22%)	
Severe renal dysfunction or pyelonephritis due to ureteric obstruction before irradiation	4/16 (25%)	7/27 (26%)	
Failed major surgery before irradiation (excluding cysto-diathermy)	3/16 (19%)	4/27 (15%)	
Effects of radiation not assessed†	5/16 (31%)	5/27 (18%)	
No regrowth of primary tumor	9/11 (82%)	19/23 (82%)	n.s.
Necrosis of bladder or bowel	8/14 (57%)	2/23 (9%)	$\chi^2=6.7$ $p<0.001$
Cumulative survival at 1 year (all cases)	2/16 (12%)	15/21 (71%)	$\chi^2=6.1$ $p<0.001$
Cumulative survival at 1 year (excluding cases with metastases or severe renal failure before irradiation)	2/10 (20%)	11/12 (92%)	$\chi^2=5.0$ $p<0.01$
Cases alive at <1 year	nil	6	
Cases surviving 2–5 years	1	7	

* T_2 muscle invaded, no mass; T_3 mobile mass; T_4 tumor fixed to pelvis.
† Dead or alive <4 months after irradiation, or inadequate follow up.

vival rate. With a change of fractionation to 6×500 rads, results have improved greatly. This is shown in Table VIII where the two fractionations are compared in 43 cases. While tumor clearance is high at 82 per cent for both dosages, necrosis of bladder and bowel dropped significantly from 57 to 9 per cent, and was accompanied by a corresponding significant rise in survival at 1 year from 12 to 71 per cent. This result is similar to that obtained for head and neck cancer (Fig. 1 and 2; Table V). Megavoltage results reported by Wallace and Payne[63] for conventional radical fractionated treatment of T_2, T_3 and T_4 bladder cancer show a 1 year survival as 50 per cent (T_2), 46.8 per cent (T_3), and 28 per cent (T_4), respectively. It is concluded that HPO does appear to greatly improve the radiotherapeutic management of advanced bladder cancer.

That this improvement is not solely due to modified fractionation is supported by the progress results of a clinical trial being pursued, with randomized cases given 6×500 rads (HPO) or 6×550 rads (Air) (Table IX). More early deaths due to recurrent tumor have appeared in the Air treated group.

RADIOSENSITIVITY OF NORMAL TISSUES BY HPO

This is, of course, a crucial factor in hyperbaric radiotherapy, and animal experimentation[9,49,55,56,65,66,67] has drawn attention to this effect. Clinical observations also suggest that certain normal tissues are relatively more radioresistant in Air than in HPO. A clinical experiment with skin showed this tissue to be more radiosensitive in anesthetized patients in HPO, and for large single β ray doses, a 25 per cent increase was tolerated in air. However, the difference is less for mucous membranes of the upper digestive and respiratory passages. For bone, cartilage and other

connective tissues large differences in sensitivity have not been observed. Two tissues we have recently studied in patients, with a view to measuring radiation damage in HPO, are the cervical spinal cord and salivary glands.

(1) *Radiation Myelitis in HPO.* In radical irradiation of head and neck disease, the cervical spinal cord and brain stem are most vulnerable structures and it is most important to have quantitative knowledge of the risk of inducing myelitis. It has been our policy to plan regional treatments of advanced head and neck tumors in HPO with a view to reducing dose to the spinal cord but this is often impossible with widespread disease. To assess the risk of myelitis, the incidence of this complication has been determined in 239 cases surviving 9 months after irradiation, and in 157 cases surviving over 12 months after treatment respectively. The spinal cord dose could be accurately determined in each case from the isodose contours. The maximum spinal cord dose was expressed as a percentage of the prescribed tumor dose to the nearest 20 per cent increment, and the n/n_0 value calculated as already described, using extrapolation numbers $m=2$ and $m=4$ respectively. There were 21 cases of myelitis. The incidence of myelitis was plotted against n/n_0, and a good linear fit was obtained, giving regressions with 95 per cent confidence limits

$$y = -0.087\ (\pm 0.044)\chi - 0.320 \text{ for } m = 2$$

$$y = -0.111\ (\pm 0.011)\chi - 0.312 \text{ for } m = 4,$$

respectively (Fig. 6).

These relationships have been used to predict the incidence of cervical myelitis in HPO. If one accepts as permissible a 5 per cent risk of inducing myelitis in cases with advanced disease of this type, the spinal cord dosage should not be higher than that shown in Table x. Of course these estimates of risk are derived from calculations based on data for 2–6 fractions only, and estimates for larger numbers of fractions (10–30) are extrapolations and assume a linearity of effect for all fractionations. It is difficult to use available published data for fractionated radiation in Air, such as that reviewed by Atkins and Tretter,[2] to test these calculations of risk in HPO extrapolated to large numbers of fractions and decide whether HPO does carry the risk of increasing radiosensitivity of the cervical spinal cord. However, Friedman's data[15] for the thoracolumbar spinal cord, gave a 10 per cent risk at a dose level of over 5,000 rads (30 daily fractions), and the

Table IX

AIR VS. HPO TRIAL IN BLADDER CANCER—PROGRESS RESULTS

	AIR (6×550 rads)	HPO (6×500 rads)
Number of cases	8	8
Stages (primary tumor)	1 T_2 3 T_3 4 T_4	1 T_2 1 T_3 6 T_4
Distant metastases	0/8	1/8
Renal failure (infection)	1/8	4/8
Postsurgical recurrence	1/8	2/8
No regrowth of primary tumor	2/8 (25%)	5/6† (83%)
Necrosis of bladder or bowel	nil	nil
Survival (Dead or Alive in months)	D_5 D_6 D_6 D_8 D_9 A_6 A_6 A_{12}	D_2* A_4 A_5 A_5 A_7 A_7 A_7 A_{10}

* Tumor with ureters transplanted, gross renal infection and dihiscence of wound prior to irradiation.

† One case died at 2 months, too early to assess,* and 1 case with cerebral metastasis was not assessed although marked regression of primary tumor was observed 4 months after irradiation.

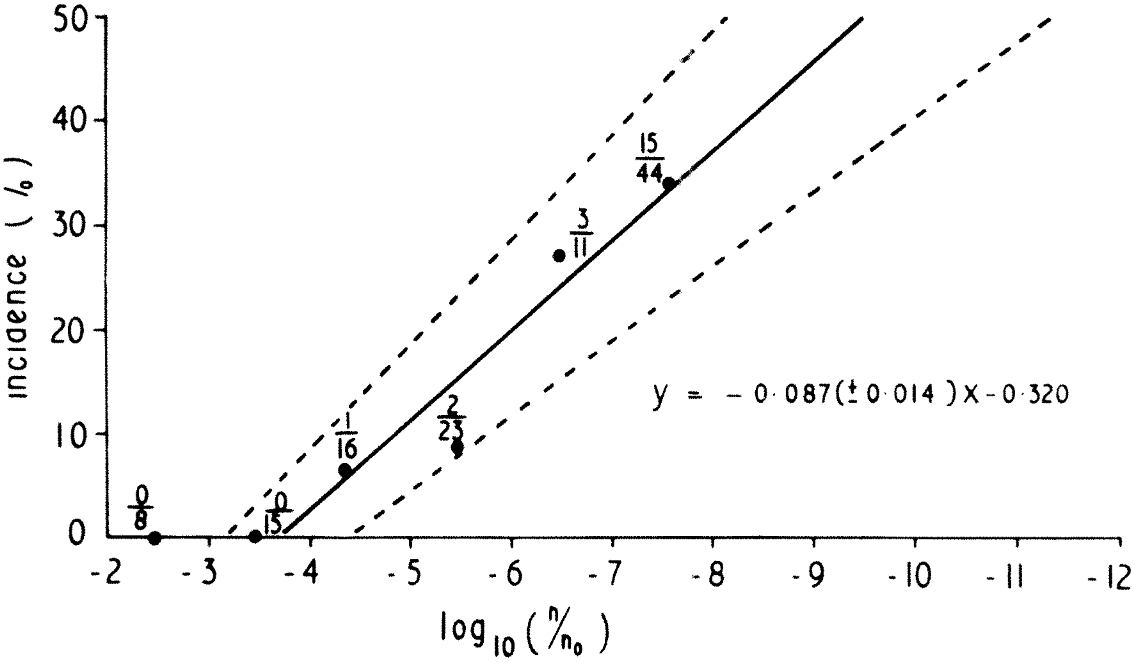

Fig. 6. Incidence of radiation myelitis of the cervical spinal cord for 4 mev. x rays in HPO plotted as a function of n/n_0 (for $D_o = 130$ rads, $m = 2$). Confidence limits shown as ± 1 Standard Deviation. Regression line ($y = -0.087\,[\pm 0.044]x - 0.320$) fitted to data by the method of least squares.

present calculations from HPO data based on $m = 2$ put a 10 per cent risk for 30 fractions in HPO at 4,050 rads, and at 6,600 rads for $m = 4$.

One can only conclude that there is, as yet, no acceptable evidence that the human spinal cord is more radiosensitive in HPO than in Air. The dose-effect calculation used in our HPO studies of spinal cord damage should be useful for assessing the risks with conventional megavoltage treatment, and these data would be necessary if radiosensitivity in Air is to be compared with that in HPO. A more detailed account of the incidence of myelitis in HPO is described elsewhere.[62]

Table X

cervical spinal cord doses (fractionated 4 mev. x ray treatments in hpo) carrying a 5 per cent risk of causing radiation myelitis

(For $m = 2$ and $m = 4$ respectively)

Fractionated Dose (rads)	Cumulative Dose (rads)
1×1,360–1,155	1,360–1,155
3× 510– 505	1,530–1,515
4× 410– 425	1,640–1,700
6× 300– 340	1,800–2,040
10× 220– 275	2,200–2,750
20× 155– 230	3,100–4,600
30× 130– 210	3,900–6,300

(2) *Sialadenitis in HPO.* An important study by Kashima *et al.*[25] has shown that exposure of the human salivary gland complex to relatively small doses of x rays caused rapid acinar cell damage and leakage of salivary amylase into the blood stream. Within a few hours of radiation hyperamylasemia results and reaches a maximum at about 24 hours after irradiation, when the serum amylase falls equally rapidly to within normal limits at about 3 days after irradiation. We have used this rise in serum amylase to measure the amount of salivary tissue remaining intact after repeated exposures of this tissue to radiation treatments in HPO.[61] Cases of head and neck cancer receiving 4×725 rads spaced at weekly intervals were studied.

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TABLE XI

SERUM AMYLASE VALUES (WOHLGEMUTH UNITS) IN CASES OF HEAD AND NECK CANCER, MEASURED IMMEDIATELY PRECEDING EACH 725 RAD FRACTIONATED TREATMENT AND 24 HOURS AFTER EACH IRRADIATION RESPECTIVELY

(Four fractions [I–IV] of 725 rads in HPO over 21 days)

	I	II	III	IV
<50% salivary glands irradiated				
(a) Before irradiation	4.7±0.8 (7)	3.6±0.6 (7)	4.1±0.7 (7)	4.0±1.0 (7)
(b) 24 hours after irradiation	110.8±29.5 (6)	66.4±11.7 (7)	10.4±2.7 (7)	7.1±2.3 (7)
>50% salivary glands irradiated				
(a) Before irradiation	3.8±0.6 (9)	3.4±0.5 (9)	3.8±0.6 (9)	3.4±0.5 (9)
(b) 24 hours after irradiation	179.0±38.4 (8)	53.6±15.2 (8)	11.7±4.1 (9)	9.9±3.9 (8)

Samples of blood were taken for serum amylase estimation immediately before each fractionated treatment and at intervals afterwards. For a single dose of 725 rads the serum amylase level (SAL) 24 hours later was directly proportional to the mass of salivary gland tissue included within the irradiated volume (Fig. 7), confirming the findings of Kashima *et al.* When the 24 hour postirradiation SAL was compared with the corresponding preirradiation value for each of 4 successive 725 rad fractions in HPO, a progressive reduction in the 24 hour value (*i.e.* the amount of enzyme appearing in the blood) occurred during the course of treatment (Table XI); even after the glandular tissues had received 2×725 rads, no further significant elevation in SAL was produced by further doses. This suggests that glandular tissue was inactivated by irradiation at a dosage level corresponding to a $n/n_0 \simeq 10^{-4}$ in HPO. There is also good reason to believe from histologic and other studies that this inactivation of salivary tissue is permanent, since cases retreated by irradiation for a second time after several months showed little or no postirradiational rise in SAL. We have tried to protect against this type of cellular damage by giving massive doses of prednisolone intravenously preceding irradiation on the hypothesis that this type of interphase cell damage is due to a destruction of membrane interfaces and a release of lysozomal enzymes. While the kinetics of postirradiation amylase release is modified by such pretreatment, there appears to be little real protection as is shown by fractionated dose studies.[61] Although we have not attempted to use this method for comparing the sensitivity of salivary tissues to irradiation in HPO with in Air, this may be a possible approach to the problem.

TUMOR AND TISSUE OXYGEN TENSION MEASUREMENTS

Many radiobiologists and clinicians are interested in studying oxygen tensions in

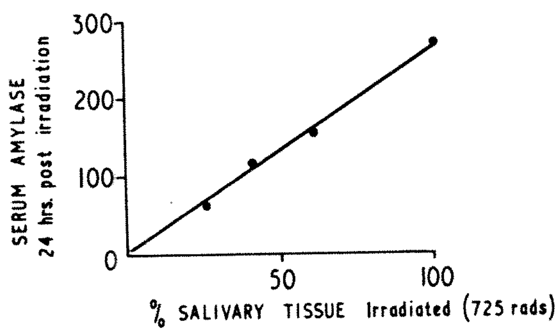

FIG. 7. Serum amylase levels 24 hours following irradiation of salivary gland tissue with 725 rads (4 mev. x rays in HPO) related to estimated mass of salivary gland tissue complex included in the irradiated volume.

tumors, either directly by using polarographic techniques or indirectly in animal experiments using microradiographic methods to demonstrate vascular patterns. The information made available so far is not unequivocal and provides no more than a rough guide to intracellular pO_2 in tissues and radiosensitivities. Our own polarographic studies in experimental animal tumors,[21] and in patients [22] subjected to HPO, have indicated: (1) that radiobiologically significant low pO_2 values of <4 mm. Hg are registered more frequently in tumor than in normal tissues under ambient conditions; (2) that HPO up to 4 ATA usually causes progressive rises in tumor pO_2 to high values but not always; (3) that rate of rise in pO_2 varies and usually the lower the electrode pO_2 value in air, the slower the rise during compression; and (4) that in HPO at 4 ATA the mean pO_2 value for 90 measurements made in large human tumors was 620 mm. Hg (a 25-fold increase), and was double the rise to 326 mm. Hg (a 12-fold increase) recorded at the necrotic centers of 23 transplanted tumors in rats. In the latter we were unable to significantly increase the value in HPO at 4 ATA by adding CO_2 at high partial pressures to oxygen under pressure,[21] although CO_2 did greatly increase pO_2 recorded in the central nervous system of rats under HPO.[23] Some animal tumor studies have suggested that fractionated irradiation causes progressive oxygenation of the tumor and that fractionation thereby reduces the need to adopt measures such as the hyperbaric technique to improve radiosensitivity.[38] A progressive fractionation schedule is also recommended, based on this hypothesis. However, similar studies of tumor microcirculatory responses to irradiation by other workers[28] yielded different results and a clinical trial from Manchester to compare a "progressive" fractionation technique with an equal increment technique, showed no difference in either cure rate or radiation reactions.[33] In the polarographic studies of pO_2 in human tumors under HPO by Evans and Naylor[13] and ourselves[22] some evidence was obtained that a previous irradiation treatment was in fact succeeded by some rise in pO_2, particularly if pO_2 values were compared when the patient was pressurized in HPO. Nevertheless, to support the thesis that fractionation *per se* oxygenates tumors, whose radioresistance is due to anoxic cells, corresponding cure rate data must be provided. In our own retrospective clinical studies of advanced malignancies, prolonged fractionated dosage to tolerance levels did not give tumor clearance rates which differed significantly from those following shorter courses of larger fractions.[58] However, for earlier disease fractionation may well be a factor which tends to improve the radiobiologic anoxia present to a lesser degree in such tumors and it would be of interest to compare results from radical courses, let us say of 4–6 fractions, with 20–30 fractions, both taken to tolerance dose levels in patients with Stage I and II disease. This information would certainly guide the so called "hyperbaricists" with design of HPO trials based on more curable material than that enjoyed to date.

METASTASES AFTER HPO TREATMENT

This important matter was raised by Johnson and Lauchlan[24] who suspected that metastases grew more rapidly in cases of cancer of the cervix uteri they treated in HPO with prolonged fractionation. A recent study of our own[60] did not demonstrate the validity of this phenomenon in head and neck disease. Experimental studies[29,47] have also been negative. However, the observation of Johnson and Lauchlan merits further investigation of suitable material. I believe that causative agents other than HPO may be involved, such as stress caused by nonspecific factors in treatment and the liberation of corticosteroids. Cogent to this possible explanation is the claim by Paterson and Russel that in the Manchester clinical trials, postoperative radiotherapy in breast cancer[31] and lung cancer[33] respectively, was associated with a higher incidence of blood borne metastases.

CONCLUSIONS

I will conclude by saying that my earlier experimental studies of oxygen effect in solid animal tumors convinced me of the reality and importance of this factor as a major cause of tumor radioresistance and that it must be of some importance to radiotherapy—a view I am sure is now generally accepted. While hyperbaric oxygen may not be the ideal technique in reversing tumor anoxia and corresponding radioresistance, it is nevertheless a practical measure which can be invoked. My own clinical experience of HPO has convinced me and others that it offers a worthwhile improvement in the results of radical radiotherapy—even if such results are to be assessed in terms of palliation and relatively short term survival rather than long term cures. The use of adjectives such as "spectacular" or "dramatic" to describe its effects hardly describes the situation and is certainly not desirable. Nor does this technique abrogate the classical disciplines of the radiotherapist in prescribing uniformly distributed doses to tumors and of a magnitude which taxes tolerance of most tissues of the body and thereby incurs significant risks of acute and chronic morbidity.

If one were to pose the question of its proven value in radiotherapy, I would suggest that the answer depends on what values are acknowledged as acceptable and to what extent proof is required. Clinical experience and early results of trials do indicate that hyperbaric oxygen improves the effectiveness of radiotherapy in causing more advanced primary tumors and lymph node metastases in certain situations such as mouth and throat and bladder to regress more frequently. Whether it would do so in earlier disease with much better prognosis after more conventional radiotherapy or surgery is not answered at present and it would be a difficult and arduous task requiring many years to establish such improved cure rates with acceptable statistical certainty. And one must remember that few clinical trials in radiotherapy so far have, in fact, established the superiority of a particular technique over another and thereby revolutionized radiotherapeutic practices. For example, one has only to draw attention to the long term clinical trials conducted in Manchester and in other leading centers, as to the value of a particular brand of postoperative radiotherapy and certain innovations, to realize how difficult it is to establish evidence of proof, sufficiently noncontroversial to be internationally accepted by practicing clinicians.

To me, a constant awareness in the clinician that the "oxygen effect" exists as a biologic phenomenon which might affect the response of a particular patient's tumor to irradiation, and that the principles of cellular radiobiology might help to consolidate the theoretic basis of radiotherapy are of utmost importance.

If HPO studies in clinical radiotherapy have done nothing more than encourage such awareness and induced the radiotherapist to lean more heavily on radiobiology, the efforts have been most rewarding, even if the clinical dividends from HPO do not appear as sufficiently exciting to merit a more widespread introduction of hyperbaric facilities to radiotherapy centers as aids to cancer treatment.

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RADIATION THERAPY ADMINISTERED UNDER CONDITIONS OF TOURNIQUET-INDUCED LOCAL TISSUE HYPOXIA*

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SARCOMAS of bone and soft tissue are considered in the radiotherapy literature as possessing a special radioresistance. Because of the opinion that radiation therapy is ineffective in the treatment of these lesions and that they are uncommon, only very limited clinical experience has been accumulated in the treatment of these neoplasms by radiation therapy.

One creditable explanation for the "radioresistance" of these tumors has been that they possess viable but severely hypoxic and hence radioresistant cells. If this were the explanation for their apparent radioresistance, then radiotherapy administered with a technique which eliminated tissue pO_2 differentials between tumor and normal tissues would be expected to achieve a greatly increased effectiveness in terms of local control of tumor for a specified likelihood of clinically significant damage to normal tissue.

A simple, direct, and relatively effective way of essentially eliminating tissue pO_2 differentials between a tumor of an extremity and the surrounding normal tissue would be to apply a tourniquet to the upper thigh or arm and thereby prevent accession of oxygen-containing blood to the part. Then, as the oxygen, present in the tissues at the time the tourniquet was applied, is utilized, the tissues would become progressively more hypoxic. According to the few studies on this subject, pO_2 of human muscle has been observed to decrease rather slowly following tourniquet application; some 20–30 minutes would be required for the pO_2 to decrease to appropriate hypoxic levels.[8,9] Some small amount of blood does pass into the extremity, despite the tourniquet, via the medullary vessels of the bone.

The present paper is an account of 6 years' experience in the treatment of sarcomas of bone and soft tissue arising in the extremities employing tourniquet produced hypoxia of the normal tissues at the time of irradiation. Progress reports of this study have appeared earlier.[4,5]

MATERIALS AND METHODS

GENERAL PLAN OF STUDY

This study was initiated in June 1961 and has been continued as a pilot or first phase study. Our first objective was to develop a safe treatment technique employing the tourniquet. Then we planned to treat a sufficient number of patients by a constant total dose and fractionation schedule to provide an indication of the effectiveness of this treatment method. If the results were to prove promising, then a clinical trial would be planned to evaluate the relative efficacy of radiation therapy administered under conditions of normal blood flow and under conditions of tourniquet produced tissue hypoxia. Our current plan is to initiate a limited trial later this year.

Although there are no "control patients" in a strict sense of the word in our material, a number of patients were seen as candidates for treatment in this study, but could not be accepted because: (1) their tumors were not located in anatomic

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sites which permitted tourniquet application, or (2) they had distant metastases. Some of these patients were accepted for radiation therapy under conditions of normal blood flow.

CLINICAL MATERIAL

In the study series (tourniquet technique) 44 patients have received a complete course of therapy at least 6 months before this writing: 22 osteosarcomas, 4 primary bone sarcomas other than osteosarcoma, and 18 soft tissue sarcomas. Two patients (designated as osteosarcomas of femur) received incomplete treatment and are not included in our tables: one developed traumatic neuropathy after tourniquet application because of uncalibrated tourniquet;[4] and a second patient fell while walking on a wet floor, producing a severe fracture through the tumor area. These patients were referred to surgery for disarticulation. In Table I are presented pertinent details of these 44 patients. As noted by inspection of Table I, the group of soft tissue sarcomas is listed under a variety of "diagnoses": 4 each of unclassified sarcoma, liposarcoma, neurofibrosarcoma, 3 rhabdomyosarcomas, 2 synovial cell sarcomas, and 1 fibrosarcoma. The age, sex, and site distributions do not appear remarkable.

"CONTROL CASES"

During the period that the tourniquet treatment has been under evaluation, 9 osteosarcomas and 4 soft tissue sarcomas have been treated by conventional therapy techniques to doses of at least 6,000 rads in 5–6 weeks. In 6 patients, a diagnosis of distant metastasis was made at the time they were seen for the primary tumor of distal extremity (5 osteosarcomas, 1 fibrosarcoma); they were treated by the same fractionation schedule as were the tourniquet technique series: 500 rads tumor

TABLE I

RESULTS OF RADIATION TREATMENT OF SARCOMAS OF EXTREMITIES UNDER HYPOXIC CONDITIONS: TOURNIQUET TECHNIQUE

Case No.	Site	Age	Sex	Radiation Dose Dose/Time/Fractions (krad/da./no.)	Appearance of Metastasis After Therapy (mo.)	Limb Function[1]	Duration of Local Control (mo.)	Presence of Intact Tumor Cells at Amputation (a) or Necropsy (n)	Present[5] Status
					I. Osteosarcoma				
1	femur	16	M	12/40/12	12	+++	>37	+(n)	D(DM)
2	femur	16	M	12/37/12	2	+++	> 8	+(n)	D(DM)
3	femur	13	F	12/36/12	2	++	> 5	+(n)	D(DM)
4	femur	16	M	12/36/12	0	0	> 6		D(DM)
5	femur	11	F	12/36/12	0	++	>10	+(n)	D(DM)
6	femur	15	M	12/36/12	2	+++	> 5	+(n)	D(DM)
7	femur	18	M	12/36/12	3	+++	> 8	+(n)	D(DM)
8	tibia	14	M	12/36/12	4	0[2]	> 8	+(a)	D(DM)
9	femur	51	M	12/36/12	>18	+++	R@12[6]	+(a)	D, I
10	femur	13	F	12/36/12	2	+[3]	> 6		D(DM)
11	tibia	17	M	12/36/12	34	+++	R@12	+(a)	D(DM)
12	femur	13	M	14/43/14	14	+[3]	R@18		D(DM)
13	femur	13	F	14/43/14	4	++	> 9		D(DM)
14	tibia	16	M	14/43/14	2	++[3]	R@8		D(DM)
15	femur	17	F	14/43/14	7	++	R@7		D(DM)
16	radius	13	F	14/43/14	4	++	>12		D(DM)
17	tibia	16	M	16/50/16	8	0	>13	−(a)	D(DM)
18	tibia	16	M	16/50/16	2	0	> 9	+(a)	D(DM)
19	femur	13	M	16/50/16	4	+	>10		D(DM)
20	femur	18	M	16/50/16	13	+++	>18		L(DM)
21	femur	21	M	16/50/16	>17	0[4]	>18		NED
22	femur	18	F	16/50/16	3	+	>10		D(DM)

Table I (*Continued*)

Case No.	Site	Age	Sex	Radiation Dose Dose/Time/Fractions (krad/da./no.)	Appearance of Metastasis After Therapy (mo.)	Limb Function[1]	Duration of Local Control (mo.)	Presence of Intact Tumor Cells at Amputation (a) or Necropsy (n)	Present[5] Status
II. Primary Bone Sarcoma Other Than Osteosarcoma									
23	tibia Ewing's tumor	26	M	12/36/12	13	o[2]	>41	− (a)	L, DM
24	femur unclassified sarcoma (suggesting liposarcoma)			14/43/14	>43	+[3,4]	>41	− (a)	NED
25	femur chondrosarcoma			16/50/16	>25	+[4]	>25	+ (a)	NED
26	foot fibrosarcoma (post excision)			16/50/16	>24	o	>11	− (a)	NED
III. Soft Tissue Sarcoma									
27	popliteal space unclassified sarcoma (two 9 cm. diameter lesions)	33	F	8/23/8	>66	++++	>66		NED
28	ankle fibrosarcoma (post excision)	14	M	12/36/12	>23	o[2]	>11	− (a)	NED
29	ankle liposarcoma (post excision)	58	M	12/36/12	>29	o[2]	>10	+ (a)	D, I
30	knee unclassified sarcoma (recurrence after perfusion)	21	F	12/36/12	34	++++	R@18	+ (a)	D(DM)
31	knee synovial (post excision)	24	M	12/36/12	>51	++++	>51		NED
32	forearm pleomorphic liposarcoma (8 cm. lesion)	61	F	12/36/12	8	++++	>10[7]	+ (a)	D(DM)
33	knee unclassified sarcoma (recurrence after excision)	69	F	14/43/14	>28	+[9]	>10[7]		L(RM)
34	forearm alveolar rhabdomyosarcoma (recurrence after excision)	77	M	14/43/14	5	+++	>12		D(DM)
35	leg rhabdomyosarcoma (post excision)	55	F	14/43/14	>31	+++	>31		NED
36	foot unclassified sarcoma (post excision)	17	F	14/43/14	3	+++	>24		L, DM
37	knee synovial (post excision)	16	M	14/43/14	>21	++++	>21		NED
38	forearm pleomorphic liposarcoma (post excision)	42	M	14/43/14	>24	++++	>24		NED
39	forearm neurofibrosarcoma (post excision)	54	M	14/43/14	>18	++++	>18		NED
40	ankle alveolar rhabdomyosarcoma (post excision)	19	F	14/43/14	10	++[8]	>14		L, DM
41	knee neurofibrosarcoma (post excision)	29	M	14/43/14	>14	++	>14		NED
42	forearm neurofibrosarcoma (post excision)	9	F	14/43/14	>12	+++	>12		NED
43	leg well differentiated liposarcoma (post excision)	55	F	14/43/14	> 8	++++	> 8		NED
44	leg	38	M	14/43/14	> 9	++++	> 9		NED

[1] Limb Function After Therapy.
o Useless limb, necrosis
\+ Walk with crutches
++ Partial weight bearing
+++ Walk with limp (no cane or crutch)
++++ Near normal.
[2] Necrosis due to short tourniquet time before start of each treatment session (see Reference 4).
[3] Fracture through tumor site.
[4] Amputation for painful limb or necrosis.
[5] D=Dead; A=Alive; DM=Distant Metastasis; L=Living; I=Intercurrent Disease; RM=Regional Metastasis; NED=No Evidence of Disease; R@=Recurrence at.
[6] Local recurrence.
[7] Amputation necessary in surgical treatment of regional lymph node disease.
[8] Superficial necrosis in biopsy scar.
[9] Subsequent amputation because of vascular failure.

dose per session, 2 treatments per week (on successive days). The other 7 patients had lesions at sites such that a tourniquet could not be applied (*e.g.*, proximal extremity, pelvis, base of skull, etc.) and were treated using the standard daily fractionation schedule.

TOURNIQUET TECHNIQUE

A full description of the treatment procedure and an explanation of the necessity for maintaining the tourniquet in place at full pressure for ≥ 30 minutes before each treatment session were given in 1965.[4] Briefly, the technique and timing which have been employed for the recent 30 patients is as follows: (1) heavy sedation achieved by intramuscular and intravenous injection of meperidine (demerol) and pentobarbital sodium (nembutal) and an intravenous infusion of 5 per cent alcohol in glucose; (2) about 1 hour after start of sedation, elevate limb for >1 minute and then fit a pneumatic tourniquet to the proximal thigh or arm and raise pressure to 550 mm. Hg or 250 mm. Hg respectively; (3) place limb inside a thin polyethylene bag, displace the air by a rapid flow of nitrogen; (4) start irradiation 30–45 minutes, by the clock, after tourniquet application; and (5) give meperidine as needed during the period of tourniquet application which should not exceed 60 minutes. The use of the nitrogen-containing bag in an attempt to reduce oxygenation of skin from the outside is considered to be of only minor importance.

RADIATION TREATMENT METHOD

Study series. The basic technique consisted of parallel opposed fields, cobalt 60 irradiation, 100–130 cm. source skin distance, and field sizes of 25–35 cm. $\times$ 10–15 cm. (except for ankle and foot lesions). The dose rate varied from ≈ 20 to ≈ 100 rads/min. (for the last 30 patients the dose rate was 45–100 rads/min.). Treatments were administered on each of two successive days for 6 to 8 successive weeks (a total elapsed time of 36 to 50 days); only one treatment field was employed on any one day.

Radiation dose. This was 1,000 rads, calculated at the mid-portion of the extremity, at each treatment; the given dose was therefore usually $\approx 1,200$ rads per session. Total radiation dose has varied from 8,000 rads in 23 days to 16,000 rads in 50 days. Out of concern for the large doses involved, the first patient received 8,000 rads in 23 days. For the subsequent 17 patients the dose was 12,000 rads in 36 days. After a recurrence had been observed in an osteosarcoma case, the dose was raised to 14,000 rads in 43 days for all cases. This dose has been continued in the soft tissue sarcomas but was raised to 16,000 rads in 50 days in the osteosarcoma series, when an osteosarcoma recurred after 14,000 rads.

Shrinking field technique. The radiation field was very generous for the first 10,000 rads, *viz.* the full width of the extremity being covered for some 25–35 cm. The fields were trimmed for the 11th and 12th treatment so that the full width of the extremity was not irradiated. For the 13th and subsequent sessions, the field size was further reduced so that only the actual site of the primary lesion was included, *i.e.*, a field size of $\approx 15 \times 10$ cm.

"Control series." These patients were also treated with cobalt 60 radiation using similar techniques (parallel opposed fields, field sizes, etc.) except that there was no planned obstruction to the blood flow to the tumor bearing part. One patient was treated with a 22 mev. betatron photon beam.

HISTOLOGIC DIAGNOSIS

Dr. J. Butler, Department of Pathology, has kindly reviewed the histologic slides prepared from the original biopsy material and amputation or necropsy material of all of the tourniquet technique treatment series except Case 35 (slides not available).

Table II

RESULTS OF RADIATION THERAPY BY TOURNIQUET TECHNIQUE
OSTEOSARCOMA

Dose (rad/da.)	Patients Treated	Dead ($\leq$12/12*)	Local Control ($\geq$12/12)	No Evident Disease at Present
12,000/36	11	8	1/3	0
14,000/43	5	1	1/4	0
16,000/50	6	3	3/3	1

* Distant metastasis but with local control.

There were several instances in which the diagnosis was revised. Case 24 had been originally histopathologically diagnosed as "osteosarcoma" (a large destructive lesion of central portion of distal femur) and has been reclassified as "unclassified sarcoma, probably liposarcoma;" in Reference 5, Table I, this patient is included as an osteosarcoma. Cases 30 and 32 of Table I of this paper were described as a synovial sarcoma and a rhabdomyosarcoma, respectively in Table II of Reference 4 (in that Table they were Cases 15 and 18); they are now considered to be an unclassified sarcoma (probably malignant melanoma) and a pleomorphic liposarcoma, respectively.

In our opinion there are so many difficulties and uncertainties in establishing the type or variety of soft tissue sarcoma that there is little merit in attempting to sort these tumors into several categories. Therefore, we have placed all of the soft tissue sarcomas into a single group. In this series of 18 tumors the diagnosis was revised in 7 cases when they were reviewed by a single pathologist. For example, a fibrosarcoma was revised to synovial sarcoma, a synovial sarcoma was revised to unclassified sarcoma, an angiosarcoma was revised to liposarcoma, a rhabdomyosarcoma was revised to unclassified sarcoma (suggesting Ewing's sarcoma of soft tissue), etc. This emphasizes the lack of security of the diagnosis with respect to a specific type of sarcoma. There were no instances of revision of diagnosis of sarcoma to benign tumor.

Further, on review of the amputation or necropsy specimen, Dr. Butler thought that intact tumor cells were present in Cases 3 and 8. These were scored as negative for tumor cells at the original pathology study and were listed as such in Reference 4 (Cases 3 and 8 in Table V). Specifically, for Case 3 the pathologist had reported only a few isolated tumor cells of "questionable viability" and for Case 8 no tumor cells were found at all. The other cases had clusters or large areas of clearly intact tumor cells and were unquestionably positive for residual cells. Significance of finding intact cells either singly or in clusters in irradiated tissue (in the absence of definite regrowth of tumor) is not established.[6]

RESULTS

NORMAL TISSUE REACTIONS

Acute reaction. Acute skin reactions following these treatments have been of modest severity; even after 16,000 rads in 50 days there was only a patchy moist reaction which was healed by 6 weeks after completion of therapy (see Reference 4 for illustrations).

Late reactions. These will be considered in reference to the usefulness of the limb as listed in Table I. The utility of the limb at 6 or more months after therapy has been rated on a 5 point scale: 0, +, · · · +++++. For a description of the function at each level refer to the footnote of Table I. The complications which developed in the 12,000 rad series have been described earlier.[4]

TABLE III

OSTEOSARCOMA TREATED BY CONVENTIONAL RADIOTHERAPY TECHNIQUE (NORMAL BLOOD FLOW CONDITIONS) USING DAILY OR TWICE WEEKLY TREATMENTS

Dose (rad/wk.)	Patients Treated	Dead ($\leq$12/12*)	Local Control ($\geq$12/12)	No Evident Disease at Present
$\approx$6,000/5–6	5	2	0/3†	0
$\approx$7,000–7,500/7	4	2	0/1‡	1§

* Distant metastasis but with local control.
† Recurrence times at 4, 14 and 17 months.
‡ Local controls at 4, 10 and 11 months; recurrence at 3 months.
§ Alive with local control of tumor but with distant metastasis present, 11 months.

At the 14,000 rad level, reactions of 18 patients may be considered. With respect to soft tissue damage (skin, muscle, vessels, nerves) there have been 5 complications: Case 24, a painful limb requiring amputation at 41 months; Case 33, peripheral vascular failure requiring amputation (poor blood supply to leg before therapy); Case 40, a superficial necrosis in excisional biopsy scar on the ankle; Case 35, a painful leg which has responded quite well to nicotinic acid and vitamin B_{12}, for the present at least; and Case 41, contracture of gastrocnemius muscle after treatment of the knee region (upper leg and distal thigh), the patient being unable to stand with both heels on the floor. Further, 3 patients developed fractures through the tumor bearing part of the bone (Cases 12, 14, and 24); and recurrence developed in Cases 12 and 14 after the fracture, which was due, in part, to failure to control the primary lesion. No fracture has occurred in any patient who has not had a primary tumor of bone. Thus, 11 of 18 patients whose tumor received 14,000 rads in 43 days have not had a complication(s) to date—note that 8 of 12 soft tissue sarcoma cases have been counted as having a ++++ to ++++ useful limb. The results were less satisfactory in the bone sarcoma patients; none being scored greater than +++ useful limb.

Eight patients have received 16,000 rads in 50 days and a significant local complication has developed in 7 of them: (1) necrosis of the soft tissues starting at the biopsy scar has developed in 4 and has been so severe that amputation was performed in all 4 cases (Cases 17, 18, 21, and 26); (2) painful limb with fixation in extension requiring amputation for relief of pain, Case 25; (3) paresis of leg, presumably due to radiation neuropathy, Case 19; and (4) severe flexion contraction, which was quite severe before therapy was started and did not improve after therapy, Cases 18 and 22. Out of this series, only Case 20 has a useful limb which is without pain or necrosis. Therefore, with our technique of achieving hypoxia and our dose schedule, 16,000 rads in 50 days is not a tolerable dose to the extremity, when large fields are employed.

CONTROL OF THE PRIMARY TUMOR

(Freedom from Clinically Evident Regrowth of Tumor)

Primary sarcoma of bone. The results of treatment of osteosarcoma are summarized in Tables II and III. Local control $\geq$12/12 indicates that the patient has survived for at least 12 months following start of therapy without local recurrence. A patient developing recurrence at any time following therapy is considered in that column. For example, after 14,000 rads 1 patient survived 12 months without regrowth of tumor and in 3 patients there were recurrences at 18, 8, and 7 months. Accordingly, for the 14,000 rad group we have listed 1 local control out of 4 patients; the patient dying at 9 months (with local control) is not included. Thus, the local control results of radiation therapy of osteosarcoma by tourniquet technique have been: 1/3 at

TABLE IV

RESULTS OF RADIATION THERAPY BY TOURNIQUET TECHNIQUE
SOFT TISSUE SARCOMA

Dose (rad/da.)	Patients Treated	Dead ($\leq$12/12)	Local Control ($\geq$12/12)	No Evident Disease at Present
8,000/23	1	0	1/1	1
12,000/36	5	0	4/5*	1
14,000/43	10†	0	9/9‡	6

* One recurrence at 18/12.
† Two additional patients have been treated at less than 6 months.
‡ One patient had amputation because of vascular failure.

12,000 rads, 1/4 at 14,000 rads, and 3/3 at 16,000 rads. These results indicate a strong dependency of tumor control response on radiation dose. Table III shows that in our series of 9 osteosarcomas treatment by conventional radiotherapy technique and dose levels (6,000–7,500 rads) was without success; a total of 4 recurrences was observed. The 7,000 rad dose produced about the same normal tissue damage as did 14,000 rads administered with tourniquet technique.

Four patients have been treated for primary bone tumors other than osteosarcoma in the study series. In this group there have been no recurrences (at 11, 25, 41, and 41 months) and only 1 patient has developed metastasis. Unfortunately, all 4 have had to have an amputation because of necrosis or painful limb. Only in Case 25 was even a good temporary clinical result achieved: a near normal limb for ≈14–16 months, later the fibrosis became quite severe and then so painful that an amputation was performed at the 25th month. Therefore, of a total of 14 patients with primary sarcomas of bone who were treated by a radiation dose of 14,000 rads or 16,000 rads, only 1 was rated as having ≥+++ limb function at 6 or more months after treatment.

From these clinical results we have concluded that radiation therapy administered according to the tourniquet technique described here is not a clinically useful treatment method for osteosarcoma.

Soft tissue sarcoma. Treatment results for the 22 soft tissue sarcomas treated by radiotherapy alone to radical dose levels at this institution since 1961 are presented in Tables IV and V. Note that in the entire experience there have been only 2 local recurrences. In the tourniquet technique treated patients local control (≥12/12) figures are: 1/1 at 8,000 rads, 4/5 at 12,000 rads, and 9/9 at 14,000 rads. These are satisfactory results especially when compared with the proportion of patients enjoying a +++ or ++++ limb function at ≥6 months after therapy: 1/1 at 8,000 rads, 3/3 at 12,000 rads* and 9/12 at

* The 2 patients who developed necrosis and required amputation, because they were in the group which had a short tourniquet time, are not counted in this tabulation; see Reference 4.

TABLE V

SOFT TISSUE SARCOMA TREATED BY CONVENTIONAL RADIOTHERAPY TECHNIQUE (NORMAL BLOOD FLOW CONDITIONS) USING DAILY OR TWICE WEEKLY TREATMENTS
(These Patients Were Treated Concurrently with the Tourniquet Technique Series)

Dose (rad/wk.)	Patients Treated	Dead ($\leq$12/12)	Local Control ($\geq$12/12)	No Evident Disease at Present
≈6,000/5	1	0	0/1	0
≈7,000/6–7	3	0	3/3*	2

* Local control at 12, 24, and 29 months.

14,000 rads. The contrast between these figures and those for the bone sarcoma patients is sharp. Similarly, the patients treated by conventional radiotherapy technique to dose levels of at least 7,000 rads have been equally good: no local failures and no complications were observed.

DISCUSSION

There are several questions posed by these results: (1) what is the basis for the markedly different local results of treatment of osteosarcoma and soft tissue sarcoma; (2) did the failure to achieve local control of osteosarcomas at dose levels producing tolerable normal tissue damage by the tourniquet technique mean that the basic premise of this study is not valid; and (3) does the use of the tourniquet technique represent an advance in the treatment of the soft tissue sarcomas?

Basic differences in cellular radiosensitivity may exist between the cells of osteosarcomas and soft tissue sarcomas, but the results presented here cannot be accepted as an indication that there is such a difference. However, the two groups of tumors in the study series were distinctive in an important radiobiologic aspect: the osteosarcomas were invariably massive tumors, an average diameter of ≈ 8 cm. (range of 4–15 cm.) with extensive destruction of bone and usually infiltration of adjacent normal tissue; in contrast, the sarcomas of soft tissue were quite small: 13 of 18 were post-simple excision without palpable tumor, 3 were 2–4 cm. diameter recurrences following excision (Cases 30, 33, and 34) and only 2 were large lesions, *viz.* 8–9 cm. masses in Cases 27 and 32. Pertinent to this point, the only recurrence that developed in this series appeared at 18 months after 12,000 rads for a proven recurrent unclassified sarcoma (Case 30). Surprisingly, our best result has been in Case 27 who had 2 lesions of ≈ 9 cm. diameter in the popliteal fossa which had recurred after wide excision and had invaded the upper tibia; despite a dose of only 8,000 rads in 23 days there is no sign of local or distant disease at more than 66 months following therapy. However, the difference in tumor volume at the time of treatment is so great between the bone and the soft tissue lesions that no comparison can be made of the "radiocurability" of the 2 tumor types using our data.

The failure to achieve local cure of osteosarcoma with doses which produce only modest damage to normal tissues strongly implies that the basic reason for employing the tourniquet technique does not apply for osteosarcoma. Had the "radioresistance" of osteosarcoma, when treated by conventional techniques and doses, been due to the presence of a small number of viable but hypoxic, and hence radioresistant cells, then an increase of dose from 6,000–7,500 rads delivered in 30–40 fractions over 6–8 weeks to 14,000 rads in 14 fractions in 6 weeks should have increased the local control rate sharply, even though it were necessary to make all of the tumor cells hypoxic.[2,7]

Pertinent to this point is a documentation that following conventional radiotherapy methods and doses, osteosarcomas are permanently controlled locally in, though small, a definite proportion of cases. Although in the small group of osteosarcomas which we treated by conventional radiotherapy methods there were no long term local controls, there are a number of examples of treatment successes in the literature. The paper of Lee and Mackenzie[3] is of special interest in that it documents 6 patients who survived 5 or more years following conventional radiotherapy for proven osteosarcoma, some of whom retained good function of the treated limb. Most of their 119 patients had amputation soon after therapy or died because of distant metastasis so that an estimate of the frequency of local control for at least 12 months following doses of 6,000–7,000 rads can not be made. But, that frequency must be substantially in excess of 5 per cent (6 of 119).

Now consider our experience with 14,000 rads delivered in 14 sessions over 43 days:

3 of 4 tumors recurred. At 16,000 rads we have not observed local regrowth of tumor but unacceptably severe late changes in the normal tissues; even so, gross tumor was observed in the amputation specimens of 2 patients (Cases 18 and 25 at 9 and 25 months, respectively). Perhaps if more vigorous attempts had been made to reduce the pO_2 even further, *e.g.*, by the procedures employed by van den Brenk *et al.*,[10] the reactions of normal tissue would have been less severe. This does not seem likely: (1) with the technique employed there is a protection of normal skin by a factor of 2.0–2.2; (2) as normal skin and muscle cannot be expected to be completely aerobic under normal condition, the effect of tourniquet application would not be expected to achieve a protection much greater than that observed here; and (3) in the 16,000 rad group, tourniquet time was $\geq$45 minutes before each session.

The severity of damage to normal tissues in these patients has been greater than need occur as a result of radiation dose alone. Four patients who required amputation for extensive soft tissue necrosis after 16,000 rads all had had large surgical biopsy scars. In 1 of these patients healing was slow; treatment was delayed 4 weeks, and was started when the healing was complete except for one small area. Necrosis has not been encountered in patients who have had small scars; *i.e.*, 3–4 cm., and which were *completely healed before start* of therapy. Unfortunately, size of biopsy scar has been out of our control as most patients have had a diagnosis established when we first saw them.

van den Brenk[9–11] has treated 11 osteosarcomas by a similar tourniquet technique using 4 mev. x rays but employing 3 dose fractions of 2,000–2,700 rads administered on either days 0, 14 and 28 or 0, 7, and 21. Seven of the 11 died because of distant metastasis but with local control at 3, 4, 8, 9, 11, 12, and 20 months; 3 have had local regrowth of tumor (6, 12, and 16 months) and 1 has had amputation at 24 months for painful limb. If van den Brenk's data on osteosarcoma were tabulated as we have our own data, then the local control results at $\geq$12/12 would be 3/6 or a value slightly better than ours for 12,000 rads and 14,000 rads. Importantly, he also observed local recurrences with appreciable frequency following dose levels that produced severe complications. In summary, a total of 33 osteosarcomas have been treated to high radiation doses employing a tourniquet technique in van den Brenk's and our series; the local results clearly demonstrate that the tourniquet technique as currently used does not represent a really effective and readily tolerated treatment method for osteosarcoma. Therefore, to the extent that pO_2 differentials between normal and tumor cells were eliminated by the tourniquet procedure, the basic premise for this study must be considered as not applicable to the osteosarcoma.

Our results in the tourniquet technique treatment of soft tissue sarcoma by radiation therapy have been extremely encouraging. This is so even though there was no palpable tumor at the time of therapy in 13 of the 18 patients. Previous experience at our institution has been that patients referred after local excision for sarcomas of the types and locations in this series will invariably develop local regrowth if left untreated.

The surgical treatment planned for each of the 18 soft tissue sarcomas had been amputation or disarticulation when the patient was referred for radiotherapy. That is, none of these patients had lesions such that a radical resection of the previous surgical site was considered feasible. Although there might have been no tumor cells in a few of the 12 cases seen post excision, achievement of local control to date in all of these 12 cases is a strong incentive to further evaluate the place of radiotherapy in the management of these lesions.* van den Brenk *et al.*[10] also observed

* Relevant to this point, mention is made of a group of 5 comparable patients who were treated by a reduced radiation dose and chemotherapy: (1) 2,000 rads$\times$2 (tourniquet technique, one dose 24 hours before perfusion and the second dose immediately following perfusion); (2) perfusion with phenylalamine mustard

a number of successes in the treatment of a similar group of sarcomas by their radiotherapy-tourniquet technique.

Of interest was the local control of 3 of 3 soft tissue sarcomas treated with $\approx$7,000 rads in 7 weeks by conventional technique (Table v). Thus, our experience in *radical* radiotherapy of these sarcomas has been a happy one to date. Also there are reports from several institutions which indicate that soft tissue sarcomas may not be so difficult to treat successfully by high dose radiotherapy, especially if combined with local resection of tumor. Atkinson, Garvan, and Newton[1] described results of treatment of fibrosarcoma by surgery alone or by 4,500 rads in 4–5 weeks followed by surgery 4–6 weeks later. They had 40 recurrences in 54 patients after surgery alone but only 1 recurrence in 15 patients treated by radiotherapy and surgery (the study was not a clinical trial). Windeyer, Dische and Mansfield[12] reviewed results of treatment of 58 fibrosarcomas with radiotherapy, alone or in combination with surgery. In their hands 6,000–8,500 rads in 5–9 weeks were often effective although a number of recurrences were observed.

Clearly, there is a need to determine for the soft tissue sarcomas, if the tourniquet technique therapy is appreciably more effective than conventional therapy and to evaluate further the place of radiotherapy in the management of these tumors.

SUMMARY

Results of radiotherapy administered under conditions of tourniquet produced hypoxia to a group of 44 sarcomas of bone and soft tissue of the distal extremities are presented.

Twenty-two osteosarcomas were treated and the local control results at $\geq$12 months were: 1/3 at 12,000 rads in 36 days, 1/4 at 14,000 rads in 43 days, and 3/3 at 16,000 rads in 50 days. Late reactions of normal tissues were so severe after 16,000 rads that the treatment method was not considered to be a clinically effective method for therapy of osteosarcomas.

Much better results were obtained in a group of 18 soft tissue sarcomas. Local control results at $\geq$12 months were 3/4 at 12,000 rads and 9/9 at 14,000 rads.

Normal tissue reactions in these patients at 14,000 rads were considered to be quite acceptable.

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and actinomycin D; and then (3) infusion with methotrexate for a week or more. Local recurrence developed in 3 of the 5. These results point out (a) that tumor cells were present at least in some of the postexcision cases and (b) the importance of a high radiation dose in treatment of the soft tissue sarcomas. These were patients of Dr. John Stehlin, Department of Surgery, M. D. Anderson Hospital and Tumor Institute.

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RADIATION DOSE-TUMOR CONTROL ASSAYS FOR IRRADIATION THROUGH A SIEVE*

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THE original conception of x-ray sieve therapy was reported early in this century by Köhler.[9] However, radiotherapy sieve technique did not become popular until after Liberson's paper in 1933,[11] when it was accepted as a means of protecting the skin and normal tissues during effective radiation treatments. Despite the striking progress in developing high energy photon beams, sieve therapy is being further studied and used because the extreme nonuniformity of dose distribution, which is a feature in this technique, is considered a benefit even in high energy radiotherapy. Becker *et al.*[1,2] applied this method to supervoltage x-ray and betatron therapy. Kaneda *et al.*[8] succeeded in obtaining a better survival rate of the patients with bronchogenic carcinoma treated by telecobalt sieve therapy than by open field telecobalt therapy.

After Liberson's paper,[11] many studies of this method were published. In these early reports, much attention was given to the problem of how skin could tolerate such large radiation doses when administered through a sieve instead of an open field. In addition, the most effective ratio of the open-to-closed area of the sieve was investigated. On the other hand, the selection of a radiation dose which would be effective in sieve therapy is based primarily on clinical experience. In this report, results of experiments will be presented which were planned to determine the relationship between tumor control frequency and radiation dose for the radiation treatment of an animal tumor by open field or by sieve technique.

Theoretic consideration of the tumor cure dose has been discussed in terms of a simple model tumor.[16] The basic idea is as follows:

Puck and Marcus[13] established that the lethal response of mammalian cells to radiation can be described by the multitarget survival curve given by the formula:

$$S = 1 - (1 - e^{-D/D_0})^m$$

where S is the surviving fraction of cells after the x-ray dose (D); D_0 is the dose which on the average yields a hit in a target and corresponds to the D_{37} or the dose which reduces S by a factor of 0.37 in the straight line portion of the survival curve; the number of targets or sensitive sites which must be inactivated to kill the cell is represented in the formula by the letter m and it corresponds to the "extrapolation number"; it may be estimated graphically by extrapolation of the straight line portion of the curve back to the ordinate intercept. When D is much larger than D_0 this formula can be simplified as follows:

$$S = me^{-D/D_0}.$$

Providing that each of the M cells in a "solid" tumor responds to radiation independently and according to this formula, the probability that a tumor will be cured is expressed as:

$$P = e^{-S.M.} = e^{m.M.e^{-D/D_0}}.^{12}$$

When P is 0.5, D is the dose which will kill all the cells in half of the tumors or, according to our model, it is the dose which will cure half of the irradiated tumors, *i.e.*, the TCD_{50}, (50 per cent local tumor con-

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TABLE I

LOCAL CONTROL OF 800 MM.³ SOLID MOUSE EHRLICH ASCITES CARCINOMA FOLLOWING LOCAL X-IRRADIATION BY SINGLE DOSES

								$TCD_{50} \pm$ S.D.
(A) *Tumors Irradiated by Conventional Method*								
Tumor Dose (rads)	3,020	3,311	3,631	3,981	4,365	4,789	5,248	
Number of Animals	6	18	24	30	22	20	12	
Tumor Control in 40 Days	0/6	5/18	8/22	20/29	12/19	17/19	10/11	
	0%	27.8%	40.9%	69.0%	63.2%	89.5%	90.9%	3,760±121
Tumor Control in 70 Days	0/6	4/18	8/22	17/27	10/17	17/19	10/11	
	0%	22.2%	36.4%	63.0%	58.8%	89.5%	90.9%	3,871±111
(B) *Tumors Irradiated by Sieve Method*								
Tumor Dose (rads)	3,736	4,365	4,842	5,370	5,957	6,607		
Number of Animals	6	16	28	20	20	12		
Tumor Control in 40 Days	1/6	6/15	17/28	15/20	13/16	10/11		
	16.7%	40.0%	60.7%	75.0%	81.3%	90.9%		4,621±209
Tumor Control in 70 Days	1/6	6/15	14/27	14/20	13/16	7/8		
	16.7%	40.0%	51.9%	70.0%	81.3%	87.5%		4,751±185

trol dose).[15] The TCD_{50} may be estimated by the use of the equation:

$$TCD_{50} \approx D_0(\ln m.M - \ln [-\ln 0.5]).$$

MATERIALS AND METHODS

Male mice of the ddY strain supplied by the Kansai Animal Laboratory, Kyoto, were used in this experiment. The room temperature was maintained at 25°C. during the experiment. The animals were housed in groups of 6 to 10 in stainless steel wire cages; wood shavings were used for bedding material. They were provided with standard purina pellets and water *ad libitum*. The experimental tumor was an Ehrlich ascites carcinoma provided by the National Institute of Radiology, Chiba. A subline of this strain has been propagated in the Department of Radiology, Kyoto Prefectural University of Medicine, since December, 1965.

An inoculum containing 10^6 cells in 50 µl. (total cell count) was injected into the subcutaneous tissue of the right thigh of 250 male mice. Beginning at 4 days after transplantation, the three diameters of the tumors were measured every day by caliper. Local irradiation of the tumor was performed on the day that the tumor diameters reached $\approx 9 \times 9 \times 20$ mm. At the time of irradiation, the mice were respiring air at one atmosphere of pressure with no known interference to the blood supply to the thigh. The doses of radiation administered are shown in Table 1. Animals were assigned to one of the dose levels by use of a random number scheme. At the time of irradiation, 6 animals were sacrificed; water displacement study of these tumors showed that the average volume was 800 (750–850) cubic millimeters.

An x-ray machine of the Toshiba KXC-18 type was operated at 180 kvp., 25 ma., with a 0.1 mm. Cu and 0.5 mm. Al filter. The half-value layer was 0.28 mm. Cu and the focus-skin distance was 18.5 cm. The dose rate was measured with a Shimazu Dose Reader at the position of the surface of the tumors and indicated a dose rate at the surface of 842 rads per minute. To permit immobilization of the mice at the time of irradiation, animals were anesthetized by intraperitoneal injection of nembutal (0.06 mg. per 1 gram of body weight). The tumor bearing thighs of 2 animals were irradiated through a 2×3 cm. square field. In order to have full scattering condition,

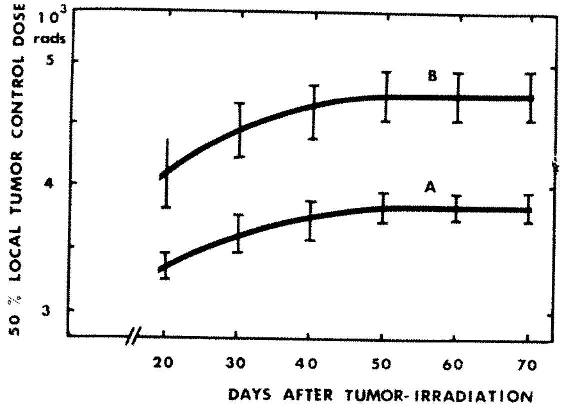

Fig. 1. Fifty per cent local tumor control doses (TCD50) of 800 mm.[3] solid Ehrlich ascites carcinoma growing in right thighs of ddY male mice is demonstrated by a conventional method (curve A) and by the sieve method (curve B).

the mouse legs were positioned on a large paraffin plate 10 cm. thick. A sieve was prepared from a sheet of lead 1.5 mm. thick with open circles of 2 mm. in diameter. The open area ratio was 50:50. The doses of radiation administered through a sieve (so-called average dose) were calculated as 50 per cent of the doses by open fields according to Schröck-Vieter's results.[14]

RESULTS

After tumor irradiation, the mice were examined every 5 days. Within 2 weeks, many tumors had disappeared and recurrences were observed during the third and subsequent weeks. If an animal had a recurrent tumor, it was scored as noncontrolled, and if a mouse died without palpable tumor before termination of the assay, the animal was excluded from the analysis of tumor cure. From the tumor control frequency obtained at each dose level, 50 per cent tumor control dose (TCD_{50}) was calculated each 10 days using "logit" analysis.[3] The results are shown in Figure 1. The TCD_{50}'s evaluated at 40 and 70 days after tumor irradiation are presented in detail in Table 1. Dose response curves at 70 days are shown in Figure 2.

Of 244 animals whose tumors had been irradiated, 91 animals had recurrences within the first 50 days after irradiation. However, almost all recurrences were observed by 40 days, and after 50 days no recurrence was observed. All surviving animals were sacrificed at 70 days.

The TCD_{50} values clearly demonstrated that if a tumor was irradiated through a sieve, a higher radiation dose was required to cure the tumor. The TCD_{50} at 70 days by open field technique and by the sieve method were $3{,}871 \pm 111$ rads and $4{,}751 \pm 185$ rads, respectively. That is, the ratio of TCD_{50} at 70 days by sieve method/conventional method was 1.23 (1.15–1.31). The ratio of TCD_{50} was constant over the time 20–70 days after irradiation.

On the other hand, the reactions of normal tissues surrounding the tumor were quite different. Epilation was complete in the irradiated area in the animals treated by the conventional method, but in the animals treated by the "sieve technique" epilation was limited to areas of the skin

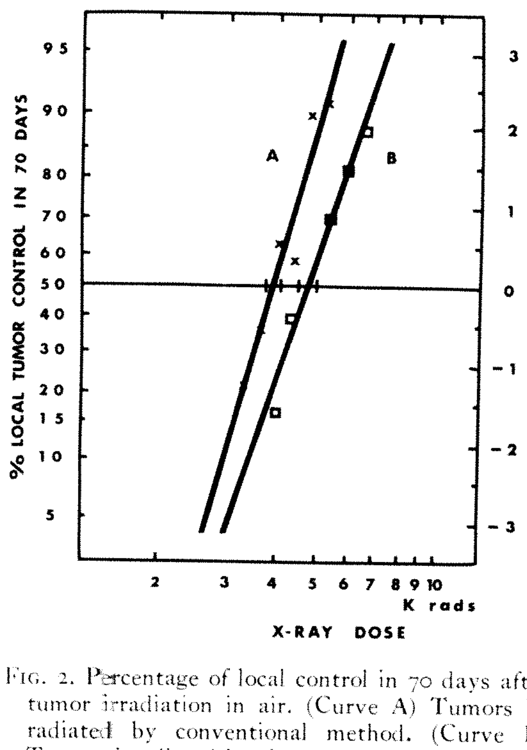

Fig. 2. Percentage of local control in 70 days after tumor irradiation in air. (Curve A) Tumors irradiated by conventional method. (Curve B) Tumors irradiated by sieve method.

exposed through the open holes of the sieve. In comparing skin retraction in animals treated by open field and sieve techniques, no gross retraction was observed in the latter group, while in the former group retraction (shortening of irradiated thigh, compared with the nonirradiated one) was observed in 1 of 4 mice that received 3,311 rads and in 8 of 8 that received 3,631 rads. This contrasts with irradiation by the sieve method; thighs irradiated to even 6,607 rads did not develop any retraction. The relative biologic effectiveness of the sieve can be assessed by deriving an estimate of the ratio of minimum radiation dose inducing skin retraction by sieve method to that for conventional open field irradiation in these experiments the ratio was >1.8. This ratio is higher than the ratio of TCD_{50} values for the two techniques, *i.e.*, 1.23.

DISCUSSION

In this experiment, the values of the m and D_0 of Ehrlich ascites carcinoma cells were not analyzed. Hornsey and Silini[5] demonstrated that the m and D_0 of the Ehrlich ascites carcinoma cells were 15 and 114 rads for aerobic conditions and 10 and 350 rads for hypoxic conditions of irradiation. Providing that D_0 for the cells of our tumors which were hypoxic were 10 and 350 rads respectively and tumors contained $\approx 5\times 10^5$ cells per mm.^{3}, and that ≈ 10 per cent of the tumor cell population was hypoxic, then surviving fraction after 3,871 rads (TCD_{50} for open field irradiation) should be 9×10^{-6}, and accordingly $\approx 4\times 10^3$ cells are presumed to have been necessary for tumor recurrence.

Radiation dose distribution throughout the tumor is markedly uneven for the sieve irradiation technique. In this experiment, the average tumor dose was calculated according to Schröck-Vieter's equation,[14] providing that the scattered dose in this small field is less than 10 per cent.[10] The TCD_{50} has been given in terms of the average dose of 4,751 rads; this would correspond to 9,070 rads (105 per cent of dose in exposed area in air) in exposed area and only 432 rads (5 per cent) in covered areas at the surface.

If the tumor m and D_0 are the same for both treatment techniques, the TCD_{50} dose of 9,070 rads would yield a S of 5.5×10^{-12} for the directly exposed cells. However, the dose of 432 rads received in shielded area would yield a surviving fraction of ≈ 0.2. Even if the minimum dose in the shielded area was 10 per cent, the survival fraction of tumor cells in that area would be ≈ 0.06. Kaneda *et al.*[7] studied the histologic changes of hair follicles of rabbit ear in exposed and in covered area, and demonstrated a relationship between the size of the open area and the minimum distances of two open holes at which any pathologic changes were not observed. According to their studies, radiation damage was observed in hair follicles in the covered area; however, if a sieve had open holes of 2 mm. in diameter and the open: covered area ratio was 50:50—only a small region was not affected by radiation. Eichhorn and Matschke[4] determined the dose distribution in "sieve" irradiated material by careful measurement in open and covered areas; their findings were consistent with the observed radiation effects reported by Kaneda *et al.*[7] Jolles *et al.*[6] succeeded in the demonstration of a "diffusible factor" which was delivered from irradiated to nonirradiated skin and could induce mitotic abnormalities.

This evidence suggests that the combination of radiation dose scattered to the covered area and the "diffusible factor" and other factors, apparently reduce the survival fraction of tumor cells in the "shielded volume" to very much less than the value of 0.2–0.06. Apparently, these and other indirect effects including immunologic reaction are quantitatively more important than during open field irradiation.

The sieve method has been described as a radiation therapy technique which affords greater protection of normal tissues from

radiation injuries, for a given likelihood of tumor cure, than obtained by standard open field irradiation. In the experimental tumor system described here, the TCD_{50} was greater for the sieve technique, but at the TCD_{50} level of effectiveness the normal tissue damage was significantly less than for open field technique.

SUMMARY

The relationship between the tumor control frequency and the radiation dose for radiation treatment of a solid Ehrlich ascites carcinoma by open field technique and sieve technique is presented.

The TCD_{50} (dose to control half of the tumor) was found to be higher for the sieve than for the open field method. The TCD_{50} (70 days) was 4,751 rads by the sieve technique and 3,871 rads by the open field technique. The ratio of TCD_{50} sieve/open field was 1.23.

The reaction of normal tissue surrounding the tumor to a dose producing a given tumor control frequency was markedly less if that dose were administered through a sieve than if through an open field. The radiation dose which induced skin retraction was >1.8 times higher by the sieve techniques than by the open field techniques.

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OXYGEN AND L-TRIIODOTHYRONINE IN RADIOTHERAPY OF MOUSE TUMORS*

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THE importance of oxygen in the cell at the time of irradiation in determining radiosensitivity is well known.[5] Methods of delivering oxygen to anoxic cells in a tumor in order to improve cure rates of radiotherapy include the breathing of pure oxygen at several atmospheres pressure[1] or of breathing 95% O_2+5% CO_2 at atmospheric pressure.[3] A trial of the gas mixture at higher pressure failed to give further improvement,[3] while pure oxygen at atmospheric pressure was no better than air[3] and changing the amount of carbon dioxide in the gas lowered the cure rate.[4]

Another method which has been tried is medication with T3. This produces an increase in rate of blood flow and in oxygen consumption which results in increased intracellular oxygen tension. There are reports on postirradiation medication with T3 in which skin damage healed more quickly but kidney damage was increased. There are also several reports on LD_{50} in animals irradiated after having been made hyperthyroid by T3 medication, in all of which the LD_{50} was reduced. But only 2 reports could be found on a trial of T3 in connection with radiotherapy of tumors. In one of these Spencer, Crummy and Vermund[7] were unable to demonstrate any increase in life span or decrease in tumor size with T3 plus roentgen therapy over roentgen therapy alone. In the second report Griem and Stein[6] conclude that some tumors in animals, but not all, respond better when T3 is added to roentgen therapy and that a trial in 4 patients also showed better results. However, no figures are given from which statistical significance could be assessed.

In view of these inconclusive data it seemed worthwhile to repeat the experiment on T3 medication in connection with radiotherapy, to compare its effectiveness with that of breathing 95% O_2+5% CO_2, and to determine whether a combination of the two would increase tumor control still further.

C3H/HeJ mice with spontaneous tumors between 8 and 15 mm. in diameter, inclusive, were used. The mice were assigned at random to one of four groups, the first being irradiated in air, the second in 95% O_2+5% CO_2 at atmospheric pressure, the third in air while receiving T3 medication, and the fourth in the gas mixture with T3. All were given 1,000 r twice a week to 6,000 r in 18 days. Methods of handling, technique of administering the radiation treatments, and of follow-up and the criterion of success have been described earlier and will not be repeated here.[2]

T3 can be administered in drinking water but it was thought that dosage control would be uncertain with this method and therefore daily subcutaneous injections were given, beginning 4 to 7 days before radiotherapy and continuing until the last day of the series. The dose was 16 μg. in a volume of 0.1 μl. per day. Spencer *et al.*[7] had tested doses from 0.25 to 2 mg./kg. and decided on 1 mg./kg., in agreement with the dose of Griem and Stein.[6] However, a preliminary trial of 25 μg. in 54 mice resulted in such severe systemic effects that less than one-third of the mice (31.5 per cent) lived to the first follow-up examination after completing treatment. On similar dosage Griem and Stein[6] had found that only 104 of 400 mice (26.0 per cent) lived to follow-up. This dose was therefore abandoned and 16 μg. substituted.

Results of treatment in all mice begin-

* Presented at the Forty-ninth Annual Meeting of the American Radium Society, Toronto, Ontario, Canada, May 29–31, 1967.
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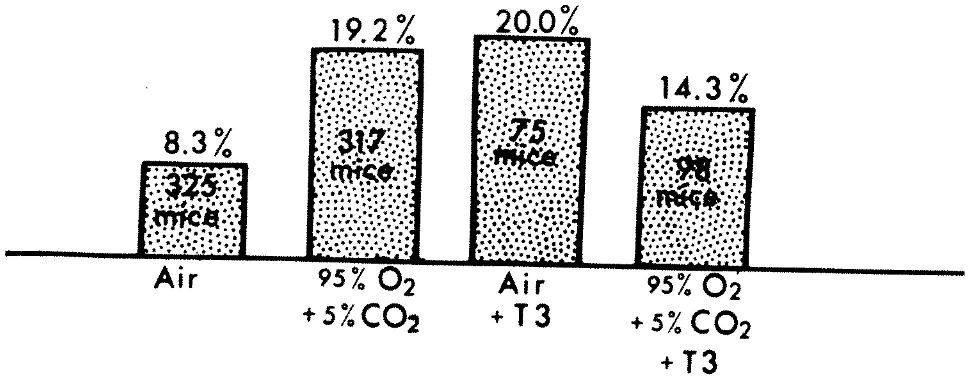

Fig. 1. Per cent of all mice beginning treatment in which the tumor could not be detected by palpation at the end of life.

ning the series are shown in Figure 1. Breathing oxygen during irradiation or either air or O_2/CO_2 after T3 medication are all superior in producing cures to breathing air without T3 medication. The lower cure rate obtained with the combination of T3 and O_2/CO_2 over that obtained with either alone was, however, unexpected. This treatment technique was therefore repeated, but with the same result. It was then thought that the explanation might lie in the fact that under this regime many of the mice died before completing the treatment series; these are all classed as failures and this might explain the poor cure rate. Accordingly, cure rates based on only those mice which completed treatment are shown in Figure 2. The T3-O_2/CO_2 combination now shows a slight superiority over either alone. While there is no statistically significant difference among the last three techniques, all show significant superiority over air.

As usual, normal tissue reactions must be examined before accepting a technique which results in more cures since it is the therapeutic ratio which determines the value of a method of therapy. Each of the first three techniques resulted in about the same fraction of mice dying during the treatment series, while the combined treatment doubled this number (from 25 to 50 per cent). This rules out T3 plus O_2/CO_2, leaving either one alone about equally effective in improving cure rates over treatment in air, without increasing systemic effects.

Another result of T3 medication is

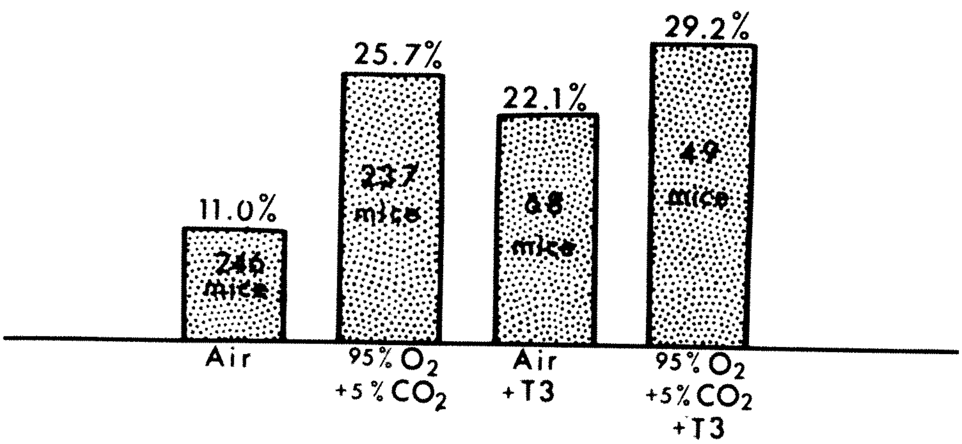

Fig. 2. Cure rates of mice completing the treatment series.

increased mitotic activity. Both the earlier reports indicate more rapid growth of untreated tumors under T3 medication. This would mean undesirable stimulation of metastases in patients. It was not possible to demonstrate this in the present experiment. Tumor sizes were the same at the time of beginning treatment whether the mice had been receiving T3 or not, but this was by design. A second, untreated tumor, presumably present but too small to detect at the beginning of the treatment series, should, if stimulated to more rapid growth by T3, appear more often by the end of the series in mice receiving this medication. It was noted that 15.5 per cent of the mice receiving T3 developed new tumors by the end of treatment and 13.7 per cent of those not receiving it developed them—essentially no difference. Perhaps these tests are not sensitive enough to demonstrate the influence of T3 on the rate of tumor growth or perhaps this dosage of T3, which is lower than that used by the earlier investigators, is too low to have this effect. Yet the dose is high enough to improve control of tumors by radiotherapy.

Both reports also indicated increased skin reactions with T3 plus radiotherapy. This observation, too, could not be confirmed in the mice since all developed such marked moist desquamation that differences in the reactions could not be detected.

Griem and Stein[6] point out that oxygen consumption is not increased to the same degree in all tissues by T3 medication, being greatest in liver, kidney, and muscle (and, apparently, from this experiment, in tumor) but little in brain, spleen, and testes. One would obtain greater increase in therapeutic ratio where the tumor lies in normal tissue not affected by T3 medication. They suggested that this method might be suitable for brain tumors and, in a trial of 2 patients, found this to be correct. On the other hand, it might give no improvement in therapeutic ratio in treating tumors lying in those normal tissues well-oxygenated by T3 medication.

SUMMARY

Mice receiving radiotherapy of breast tumors, after having been made hyperthyroid by T3 medication or while breathing 95% O_2+5% CO_2, showed an increased cure rate over mice treated while breathing air, but without increased systemic effects.

When both T3 and O_2/CO_2 were used, the death rate during treatment was doubled and the cure rate no further improved.

In some situations T3 medication may be superior to oxygen at high pressure as a means of improving oxygenation of tumor cells during radiotherapy, while in other situations it may be inferior.

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The cytomel used in this experiment was supplied through the courtesy of Smith Kline & French Laboratories.

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RADIATION SENSITIVITY OF SPLEEN CELLS IRRADIATED *IN VITRO* AND *IN VIVO**

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THE radiosensitivity of cells *in vivo* is generally regarded to be similar to cells *in vitro*. Extensive clinical interpretations have been drawn from these assumptions although direct evidences on this view are few and limited to systems wherein simultaneous assay is possible. The present study reports experiments describing some limitations as studied with spleen cells and measured by spleen colony-forming ability.

Till and McCulloch[17] described a class of cells representing a small proportion of the nucleated cells of isologous hematopoietic tissues which possess the capacity of forming spleen nodules (colony-forming units or CFU) upon transplantation into heavily irradiated mice, or into mice afflicted with the WW^v trait.[8]

Siminovitch *et al.*[14] studied several properties of CFU of different tissue origin. The CFU of bone marrow, spleen or fetal liver and spleen were shown to exhibit different responses, which led them to postulate that the CFU are not necessarily a homogeneous class of cells. Koukalová and Karpfel[6] have also found differences in proliferative ability and radiosensitivity with donor age. Hanks[4] has shown the migration of bone marrow CFU to the spleen indicating at least a one-way traffic between two different sites, and also suggesting a continuous migration of cells between the different hematopoietic tissues. Siminovitch *et al.*[14] found differences in radiation response for colony-forming cells from different sources.

McCulloch and Till[7] studied the radiation sensitivity of CFU of bone marrow origin *in vitro* and *in vivo*. CFU radiosensitivity was found to be different under these two conditions. We have studied the radiosensitivity of spleen cells obtained from adult mice as measured by colony-forming ability. The results show that CFU radiation responses *in vivo* and *in vitro* are not identical. However, for the colony-forming cells of spleen origin, the responses differ from those reported for bone marrow CFU to Co^{60} γ rays.

MATERIALS AND METHODS

MICE

Male and female mice of inbred C3H(Z) strains were used in these experiments. They were between 2 and 4 months of age at the time of experimentation. All donors and recipients were from the same inbred colony.

PREPARATION OF CELL SUSPENSIONS

Spleen cells were prepared from the spleens of several matched donor animals. Donors were heparinized with 100 U.S.P. units of heparin given intraperitoneally, and approximately 10–15 minutes later were sacrificed using cervical dislocation. The spleens were then excised, trimmed free of adventitia, minced into small pieces, washed several times with ice-cold Hanks' solution, and then either passed through a 40-mesh stainless steel wire cloth, or gently dispersed using a chilled tissue grinder. Single cell suspensions were obtained by passing the crude suspensions through small gauge needles. Nucleated cell density was determined by direct count in a he-

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mocytometer using phase contrast microscopy following lysis of red blood cells with 1 per cent acetic acid. Cells for injection were prepared by dilution using Hanks' solution supplemented with 5 per cent fetal bovine serum.

WHOLE BODY IRRADIATION OF RECIPIENTS

Recipients of cells were initially x-irradiated using an x-ray unit operated at 220 kv., and at 15 ma. with added filtration yielding a beam of half value layer of 0.9 mm. copper. The dose rate was 66 rad/min. at 60 cm. focus skin distance. Whole body doses of 610–950 rad were delivered before transplantation of cells.

CELL IRRADIATION *in vitro*

In vitro cell irradiation was done in plastic Petri dishes using the above unit, with full back-scatter. Dose rates were measured* using a National Bureau of Standards calibrated Victoreen r-meter, and the absorbed dose was measured directly using lithium fluoride (LiF).[1] In each experiment common stocks of cells were prepared, from which separate aliquots were drawn for each radiation dose. An identically treated unirradiated sample was used for the control. Cell suspensions were irradiated at ice temperature after equilibration with air or 100 per cent oxygen gas. The dose rate was 68 rad/min.

CELL IRRADIATION *in vivo*

Irradiations were done using a lucite, pie-shaped irradiation unit which permitted irradiation of 10 animals simultaneously, each animal in an individual slot. They were symmetrically placed about the center of the field, and the unit rotated continuously during irradiation. It was provided with full back-scatter. Dose rate measured at the mid-level of the mouse was 65 rad/min. There was a ±2.5 per cent variation from mid-plane dose to the top or the bottom of the animal as measured in a paraffin phantom mouse with LiF.

* I thank V. C. Moore and M. T. I. Hilger, Radiological Physicists, University of Minnesota and A. Feldman, Radiological Physicist, Mayo Clinic, for assistance in these measurements.

TABLE I

RESIDUAL ENDOGENOUS COLONY-FORMING UNITS (CFU) WITH DIVIDED RADIATION DOSES *in vivo**

D_1† (rad)	D_2† (rad)	Endogenous CFU (mean no. ±S.E.)
610	460	0.25±0.13
610	460	0.18±0.08
610	322	0.00
665	302	0.60±0.22
665	337	0.11±0.10
665	337	0.22±0.14
705	277	1.71±0.70
800	139	0.25±0.13
	Average	0.42

D_1, D_2 = First and second whole body doses of x-irradiation.
* Spaced about 1 day apart.
† Average dose in rad.

ASSAY FOR SPLEEN COLONY-FORMING CELLS

For Cells Irradiated in vitro: Irradiated and unirradiated cells were injected intravenously into the tail vein of prewarmed recipients which had received 900–950 rad shortly before. Surviving animals were sacrificed 8–10 days after cell injection, their spleens excised, placed in Bouin's fixative and spleen nodules visible by eye counted after fixation.

For Cells Irradiated in vivo: Animals were irradiated with various large x-ray doses one day before receiving the cells. On the following day, the spleen cells were prepared, and graded numbers injected intravenously. Two hours after cell injection, the animals received a second x-ray dose which irradiated the recently transplanted spleen cells and destroyed the remaining endogenous CFU (Table 1). The combined total whole body x-radiation dose was sufficient to produce endogenous CFU to less than 0.5 and was about 900–1,000 rad for all recipients. All survivors were sacrificed 8–10 days later, their spleens excised, fixed in Bouin's and the nodules counted.

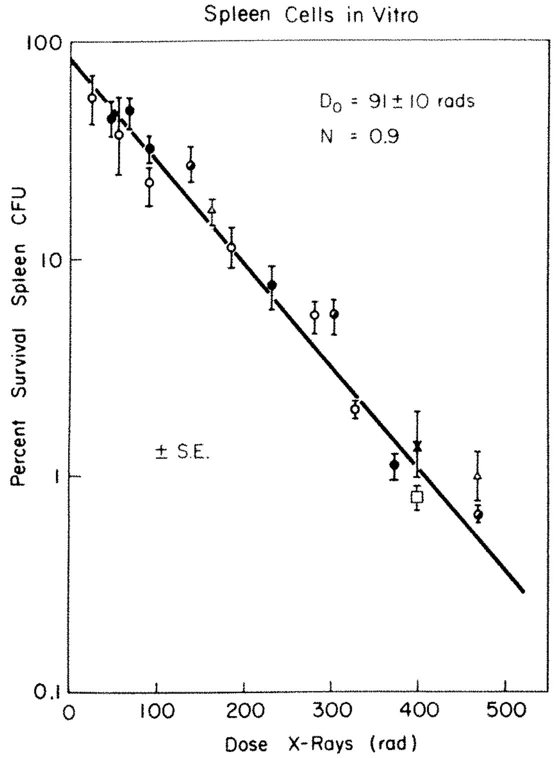

FIG. 1. X-ray survival curve for spleen cells irradiated *in vitro* and assayed for spleen colony-forming ability *in vivo*. Vertical bar represents the standard error of the data point. Different symbols denote separate experiments.

RESULTS

RADIATION SENSITIVITY OF SPLEEN COLONY-FORMING CELLS *in vitro*

Cell radiosensitivity was determined by the ability of the colony-forming cells of the nucleated cell population to form a visible spleen colony. When cells were irradiated prior to transplantation, there was a loss in their ability to give rise to visible spleen colonies. A dose-response survival curve (Fig. 1) is shown for the loss of colony-forming units as a function of x-ray dose for the irradiated cells. The survival curve for spleen cell CFU exhibits a near exponential curve with a D_0 of 91 ± 10* rad and an extrapolation number of 0.9.† (The latter value was not statistically significantly different from 1.0.)

RADIATION OF SPLEEN CELLS IN LIVING ANIMALS

Six animals were irradiated at the same time with 200 rad. They were sacrificed immediately afterwards, their spleens excised and placed on ice. Three spleens were pooled to make a cell suspension and the others individually converted into cell suspensions. Inocula containing 5×10^6 cells (determined by replicate counts before and after preparation) prepared from the several spleens, were injected into 15 heavily irradiated recipients. Eight days later survivors were sacrificed, their spleens excised and nodules counted after fixation in Bouin's fixative. The results (Table II) show variation between the results obtained from the different donors, and from the pooled spleens. The results suggest that the CFU density of spleens varies considerably, or that there is variation in sensitivity of the CFU residing in the spleen. It is known that CFU density varies between experiments using pooled spleen cells (Table III). Irradiation of small groups of donors also led to results with a great deal of variation. Hence, it was decided to use the method described by McCulloch and Till[7] starting with a common pool of cells, and irradiating the transplanted cells *in vivo*.

TABLE II

SPLEEN CELL IRRADIATION (200 rad) *in vivo*: SAMPLING VARIATION FOR DONORS IRRADIATED SIMULTANEOUSLY

Group	Source	Cell Dose	Spleen CFU (mean no. ± S.E.)
1	Pooled spleens from 3 donors	5×10^6	3.5 ± 1.2
2	Single donor	5×10^6	3.9 ± 1.1
3	Single donor	5×10^6	13.8 ± 3.8
4	Single donor	5×10^6	6.4 ± 0.3

* 95% confidence limits.

† The loss of colony-forming ability declined with dose according to the relationship: $S = 1-(1-e^{-D/D_0})^n$; where S = surviving fraction, n = extrapolation number, or zero dose intercept with ordinate axis, D_0 = dose to reduce survivors to 0.37 on the exponential curve, and D = radiation dose.

RADIATION SENSITIVITY OF SPLEEN COLONY-FORMING CELLS *in vivo*

The dose response survival curve for cells irradiated *in vivo* 2 hours after transplantation and assayed by spleen colony-forming ability is shown in Figure 2. The lower curve, shown as a dashed line, represents the survival curve for cells irradiated *in vitro* (Fig. 1). The upper curve shows the results obtained in several experiments where the spleen cells were irradiated *in vivo* following transplantation. All irradiations were done 2 hours after cell transplantation. A least squares analysis of the data points for the exponential portion of the curve yielded an average D_0 of 109±13 rad and an extrapolation number of 1.2 for the pooled data. Statistical analysis of the slope differences for cells *in vitro* or *in vivo* indicated that they were significantly different (P=0.024). The difference of the extrapolation numbers was not significant at the 5 per cent level (0.5>P>0.1) although the average results obtained *in vivo* were higher than those obtained under *in vitro* irradiation conditions.

The average results may be described by the above parameters. However, it was noted that although the results of a single experiment were usually internally consistent (results obtained in a single experiment denoted by one set of symbols), there was variation between experiments (Fig. 2).

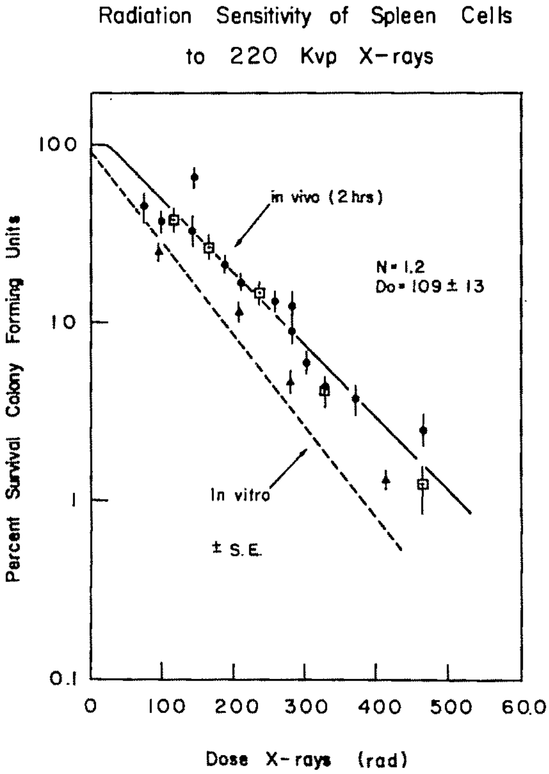

FIG. 2. X-ray survival curve for spleen cells injected intravenously irradiated *in vivo* 2 hours after cell transplantation and assayed by spleen colony-forming ability. Vertical bar represents the standard error. Different symbols denote separate experiments. Dashed line shows the results for spleen cells irradiated *in vitro*.

TABLE III

CFU DENSITY (CFU/10^5 NUCLEATED CELLS) OF DIFFERENT POOLED SPLEEN CELL SUSPENSIONS*

Exp. No.	CFU/10^5 Cells±S.E.†
1	1.5±0.1
2	3.2±0.4
3	2.5±0.4
4	1.9±0.2
5	3.0±0.4
6	0.8±0.1
7	0.6±0.1
8	2.1±0.6
9	1.6±0.4
10	1.6±0.2

* Representative results from 10 separate experiments.
† Not corrected for endogenous CFU which were less than 0.5.

EFFECT OF OXYGEN BREATHING ON CELL RADIOSENSITIVITY *in vivo*

As the most rapid changes in radiosensitivity are brought about by hypoxia, and in view of the recent intravenous injections of cells which may have produced lung emboli and hypoxia, the following experiment was performed. Two sets of partially irradiated (760 rad) animals were injected with 3×10^6 spleen cells prepared in the usual manner. At 2 hours, they received a radiation dose *in vivo* of 185 rad, one group while breathing air, and the other while breathing 100 per cent oxygen gas. Gas was flushed into a plastic bag which loosely

Table IV

EFFECT OF OXYGEN GAS (100%) BREATHING ON CFU RADIOSENSITIVITY *in vivo* (185 rad) TWO HOURS AFTER CELL INJECTION

Group	Gas Treatment	Cell* Dose	CFU (mean no. ± S.E.)
1	Air	3×10^6	16.4±4.4
2	O_2 100%	3×10^6	15.0±2.9

* Common cell suspension.

surrounded the irradiation holder, at a flow rate of 6 liters/minute. The results of the experiment (Table IV) show little, if any, effect which could be ascribed to oxygen deprivation.

DISCUSSION

Cellular radiobiology and its relevance to tumor radioresponse *in vivo* has evolved from the tissue culture x-ray survival curves reported by Puck and Marcus[11] for cells *in vitro*. Hewitt and Wilson[5] with an *in vivo* bioassay of viable mouse leukemia cells have shown that tumor cell response *in vivo* was similar to cultured cells, and Till and McCulloch[17] have reported that normal mouse bone marrow cells also respond similarly. These studies have tended to equate cell radioresponse *in vivo* to cell response *in vitro*.

McCulloch and Till[7] and Williams and Till[19] have, however, reported a lack of agreement for cells of similar origin when irradiated *in vitro* or in the intact animal. For malignant tumor cells, even in isologous systems, host-resistance may contribute to tumor radiation response.[9] In addition, dilution assays possess inherent limitations of accuracy,[9] and clonal assays suffer from their selective nature favoring the more rapidly growing cells, before the more slowly growing cells can grow to visible size.[15] All of these factors may contribute to the agreement or lack of agreement in radiosensitivity for cells irradiated *in vivo* and *in vitro*.

We have found that spleen cell radioresponse determined by spleen colony-forming ability does not show agreement when irradiated *in vitro* or *in vivo*. However, the results reported here show an effect opposite from that reported for bone marrow cells to $Co^{60}\gamma$ rays.[7] With bone marrow it was found that cells *in vitro* were less radiosensitive compared to cells *in vivo*. Spleen cells in these experiments were less radiosensitive *in vivo*. Other investigators,[5,13] working with transplantable mouse leukemia or sarcoma cells,[2] have shown the cell radiosensitivity to be the same. However, a dilution assay was used compared to the clonal assay used in this report. Siminovitch *et al.*[14] regarded the differences in the properties of colony-forming cells of the various tissue origins, as suggestive of heterogeneity of cell types. These differences may not reflect a heterogeneous class of cells, but rather the fact that the same cells may be in a different physiologic phase of the life cycle when they reside in different tissues. The temperature at which the cell irradiations were done may also be important. *In vitro* irradiations were performed with cells at 0–4° C. *In vivo* radiation conditions were at 37° C. (Homeostatic mechanisms maintain a constant body temperature.) Under such conditions, the mechanism proposed by Phillips and Tolmach,[10] and by Whitmore and Gulyas[18] may operate. That is, irradiation produces "potential" lesions within the irradiated cell. Such lesions may either be fixed giving rise to a lethal event or be repaired. The differences observed with spleen cells in these experiments are consistent with the interpretation that for irradiation *in vivo*, repair processes predominate for the spleen cells. For bone marrow cells, the progression to fixation is apparently the predominant process. Still another possibility is suggested by the higher extrapolation number observed *in vivo* than under *in vitro* irradiation conditions. Thus, recovery processes involving extrapolation number of the type described by Elkind and Sutton[3] might also be pres-

ent. The transplanted cells may also interact with those in the tissues in which they are deposited, contributing to their improved survival.

On the basis of these experiments the question is not entirely resolved. However, noteworthy is the temperature shift which was part of the protocol of these experiments. Rao and Engelberg[12] have recently studied the effects of temperature on the cell cycle. Of the various possibilities, we believe that the process of cell harvesting and transplantation may have altered cell progression through the cell cycle. Terasima and Tolmach[16] have shown, using synchronized HeLa cells, that radiosensitivity varies with cell age. Similar radiosensitivity fluctuations have been observed in other experiments following transplantation. This suggests that CFU radiosensitivity may not be constant during the early period following transplantation, but instead pass through multiple different states.

SUMMARY

X-irradiation survival response by colony-forming ability was determined for mouse spleen cells. Cells irradiated *in vitro* or *in vivo* differed in their radiosensitivity and cells irradiated *in vivo* were less sensitive than cells irradiated *in vitro*. The differences appeared to be due to a difference in the slope or D_0 of the survival curve. D_0 *in vivo* was 109 rad, and *in vitro* was 91 rad. Oxygen breathing did not alter radioresponse. The extrapolation of cell radioresponse observed *in vitro* to the *in vivo* situation may be limited under certain circumstances.

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Mary Bilek, Biometrics Division, provided assistance with the statistical analysis of the data.

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LETHAL EFFECT AND VISIBLE IRRADIATION DAMAGE*

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As is well known, the older the organism, the more resistant its tissues are to radiation. One classical example of decreasing radiosensitivity with increasing age is provided by the insect *Drosophila*. The lethal dose for this insect is 190 r for eggs, 1,300 r for larvae, and 100,000 r for adults.[15,16] Varying sensitivities to roentgen irradiation also occur in amphibians, particularly in the salamander known as the Mexican axolotl (*Siredon mexicanum*). The differences in the sensitivities of axolotl larvae 5, 10, 20, and 30 days subsequent to hatching are remarkably great, each day of age being important.[20]

The general opinion is that it is easy to suppress mitotic activity and to damage various tissues in a young organism by means of radiation. What, however, are the relationships between the ability to survive irradiation, the suppression of growth, and radiation damage? According to Carlson,[10] for instance, "Cells vary enormously in their ability to survive ionizing radiation, and this seems to have no relation to the mitotic effect of the radiation. It requires, for example, 72 r to depress mitosis in cells of the developing rat retina to approximately the same extent as 8 r depresses it in the grasshopper neuroblast. On the other hand, 72 r kills approximately 11 per cent of the developing rat retina cells as determined 6 hours after treatment, while 10,000 r produces virtually no deaths of grasshopper neuroblasts within at least 8 hours after treatment."

What will be the results of irradiating young axolotl larvae with various doses, including both lethal and nonlethal doses? It is not easy to answer this question, since it is necessary first to know the minimum dose that will really kill the animals, as well as the latent periods both for the organism as a whole and for the individual tissues. In particular, two factors must be taken into consideration: the size of the dose and the age of the irradiated animals.

A previous investigation[3] utilized axolotls 30 and 47 days after hatching. The present study, however, utilized axolotls 12 days after hatching. There is a good deal of difference between axolotl larvae 12 days and 30 days of age. The latter are 3 or 4 times as large and have 4 limbs, whereas the former have only the 2 anterior limbs. The previous investigation involved only 2 doses: 3,000 and 6,000 r, respectively. The purpose of the present study is to demonstrate the relationship of lethal effect to growth suppression and visible radiation damage after irradiation with various doses ranging from 100 to 3,000 r.

MATERIALS AND METHODS

The present study utilized 650 axolotls (*Siredon mexicanum*), 12 days after hatching. In one series of experiments involving 500 animals taken from one spawning, nine groups of 50 animals each received total-body irradiation with 200, 300, 400, 800, 1,000, 1,500, 2,000, and 3,000 r, respectively. In another series of experiments involving 150 animals taken from another spawning, two groups of 50 animals each received 100 and 200 r, respectively. In each series of experiments, the remaining 50 animals served as untreated controls.

Irradiation conditions were as follows: 100 kv., 5 ma., 0.25 mm. Al filter, beryllium

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window roentgen-ray tube, and target-object distance 20 cm. Under these conditions, the intensity was 299.5 r/min. During irradiation, the animals were in a minimal amount of water, a layer about 3 to 4 mm. thick, in a plastic box 4.5×4.5×1.5 cm. Immediately after irradiation, the animals were put into fresh water.

The mortality rate was very high even after irradiation with the lowest doses. Most animals still alive when it was time for fixation were already dying. Animals were fixed in Stieve's acetic acid solution of mercuric chloride and formaldehyde[17] for histologic study. The material was embedded in paraffin containing 5 per cent beeswax, and was sectioned at 8 μ. Sections were stained with Ehrlich's hematoxylin and eosin, and photomicrographs were made under low (× 170) and high (× 570) magnifications.

RESULTS

GROWTH SUPPRESSION AND LETHAL EFFECT

Definite data concerning the effect of 100 r on growth were not provided by the present study. All other doses from 200 r up, however, very definitely suppressed growth. This effect is obvious in growth curves (Fig. 1) and in photographs of irradiated and control animals (Fig. 2,*A–D*). Growth and development were almost completely suppressed even by doses as small as 200 or 400 r. Differences between animals irradiated with 400 r and control animals were evident as early as 13 days after irradiation (Fig. 2, *A* and *C*), but very much more so 17 days later (Fig. 2, *B* and *D*).

It was surprising to find that almost all of the irradiated animals died within the first month after irradiation, only 2 animals

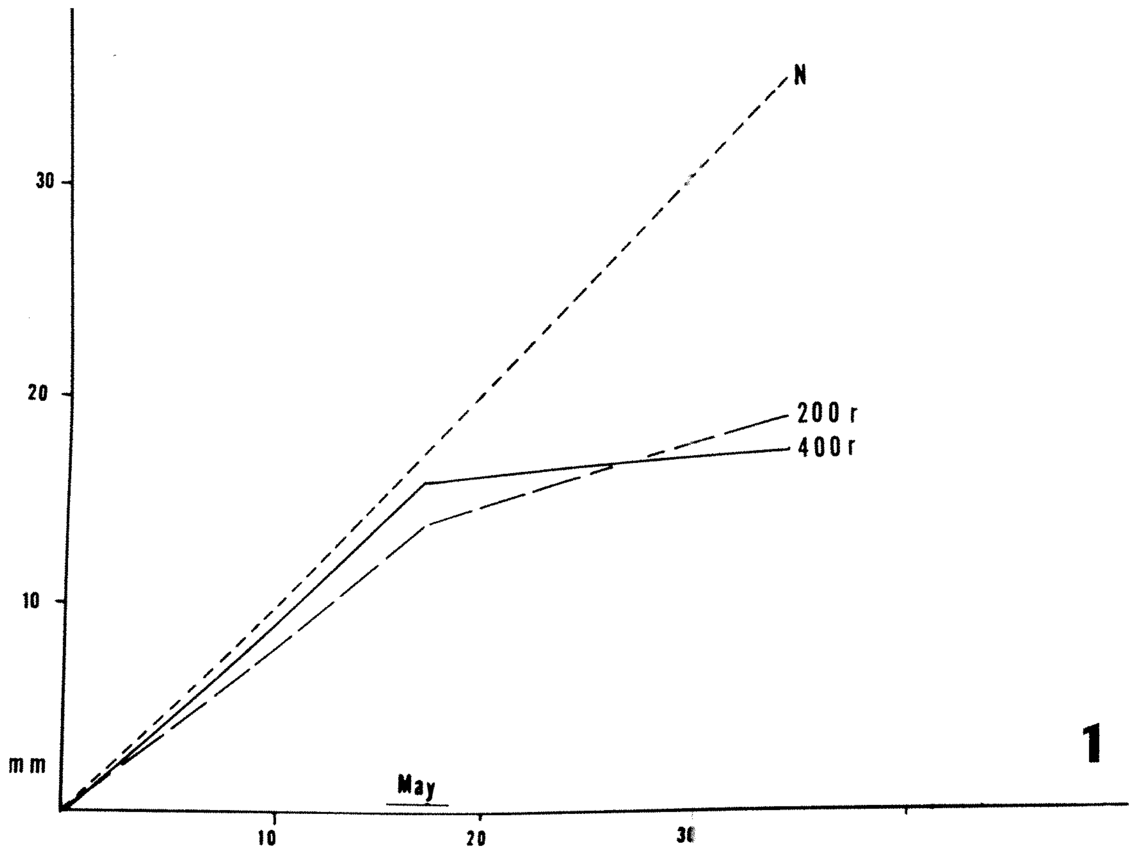


Fig. 1. Suppression of growth of young axolotls irradiated with small doses (200 and 400 r). N, growth of normal (unirradiated) larvae. Ordinate: sizes of larvae in mm. Abscissa: period of observation.

Fig. 2. Effects of irradiation with 400 r on growth and development of young axolotls. (*A*) Irradiated larvae 25 days after hatching (irradiated 12 days after hatching). (*B*) The same animals 17 days later. (*C*) Normal (unirradiated) larvae 25 days after hatching. (*D*) The same animals 17 days later.

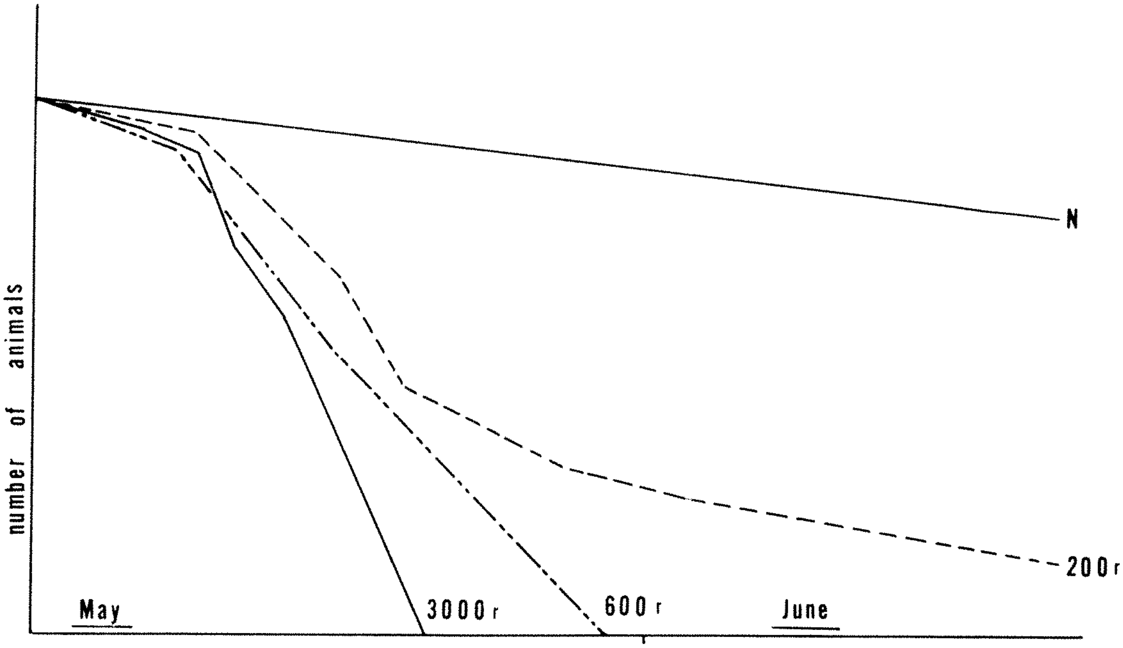


Fig. 3. Lethal effects of irradiation with various doses: 200, 600, and 3,000 r. Ordinate: numbers of animals surviving. Abscissa: period of observation. N, number of normal (unirradiated) animals.

(2 per cent) surviving after 200 r and only 4 (8 per cent) after 100 r. The lethality of the doses used is thus obvious. Especially noteworthy is the fact that the great majority of animals irradiated with more than 100 r died on the 5th or 6th day after irradiation (Fig. 3). It should also be noted that the deaths of the last animals surviving irradiation with 600 and 3,000 r were separated by only 9 days, and the deaths of the last animals surviving irradiation with 800 and 3,000 r were separated by only a single day.

HISTOLOGY OF UNIRRADIATED LARVAE

Before radiation damage in axolotls can be evaluated appropriately, it is necessary to take into consideration the histologic peculiarities of control axolotls of the same age. These peculiarities are highly important in this regard, since one of the normal characteristics of certain tissues in these animals is variability, and any attempt at evaluating radiation effects without knowing the normal range of variability is ill advised, to say the least.

Generally the skin epithelium of the body and tail of normal axolotls is simple squamous epithelium (Fig. 5*A*). In some regions, however, the skin epithelium is commonly transformed into stratified squamous epithelium; on the head, in fact, this is the rule (Fig. 4, *A*, *B* and *E*).

Variation in other tissues and organs may be considerable. The size of the nuclei of liver cells, for example, tends to differ from one normal axolotl to another. Liver-cell nuclei are comparatively large in some individuals (Fig. 4*C*), but much smaller in others.

Lymphatic tissue, particularly of lymph nodes, develops gradually, and even such typical lymphoid tissue as the peripheral portion of the liver can be observed only towards the end of the first month. In contrast, organs such as the olfactory chambers (Fig. 4*B*) and the eyes (Fig. 8*D*) are clearly differentiated into their characteristic structures even in small larvae. The presence of large blood vessels and many small blood vessels is typical (Fig. 4 *D*).

HISTOPATHOLOGY OF IRRADIATED TISSUES

Skin Epithelium. Changes in the skin

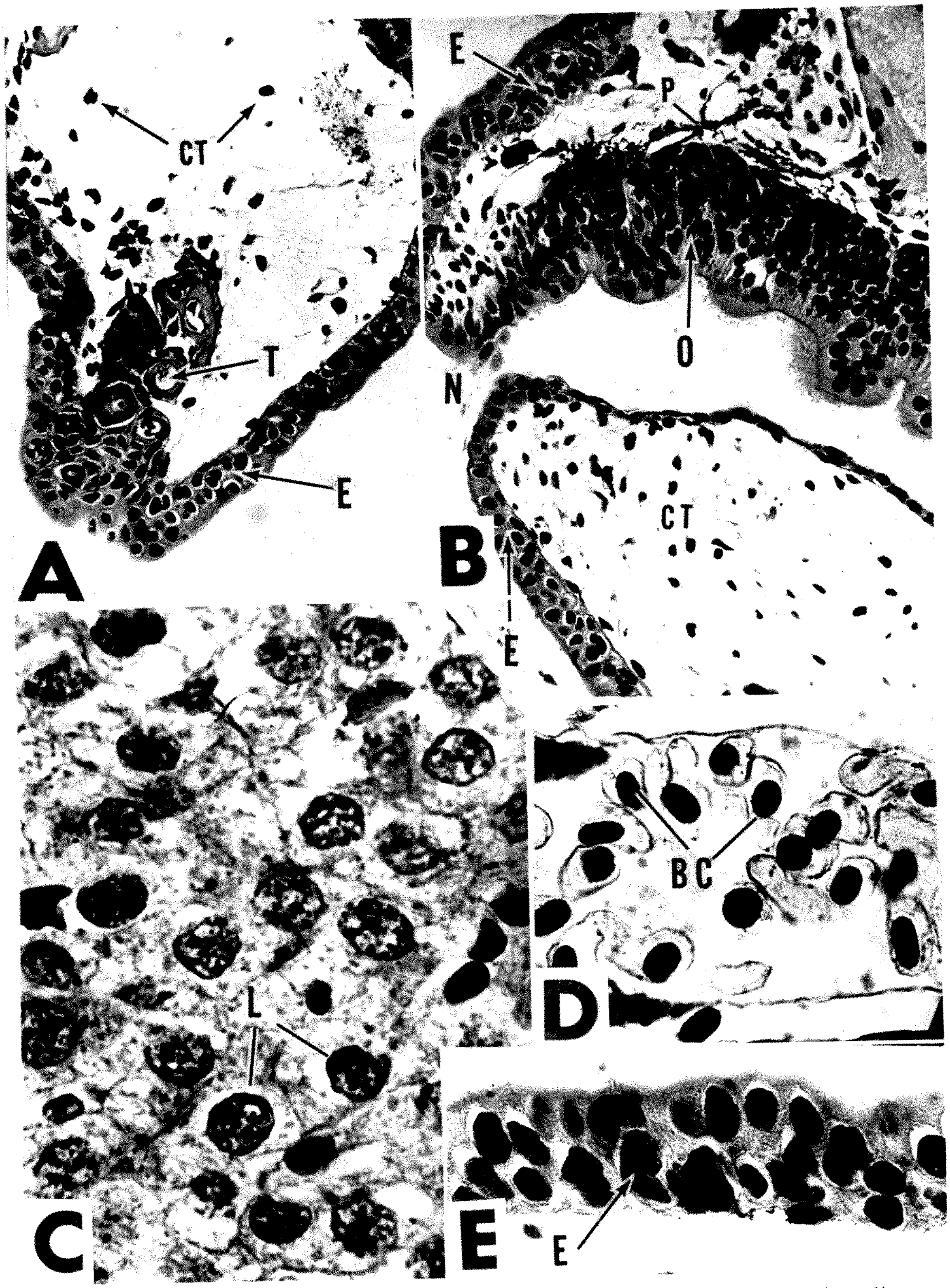


FIG. 4. Histology of normal (unirradiated) axolotls. (*A*) Part of sagittal section through lower jaw of larva 35 days after hatching. CT, cells of loose connective tissue; E, skin epithelium; T, tooth anlage. Photomicrograph ×170. (*B*) Part of frontal section through head of larva 35 days after hatching. CT, loose connective tissue; E, skin epithelium; N, nostril; O, olfactory epithelium; P, pigment cell. Photomicrograph ×170. (*C*) Part of frontal section through liver of larva 41 days after hatching. L, nuclei of liver cells. Photomicrograph ×570. (*D*) Part of frontal section through body of larva 33 days after hatching. BC, blood cells in large blood vessel near liver. Photomicrograph ×570. (*E*) Part of frontal section through head of larva 35 days after hatching. E, nuclei of cells of skin epithelium. Photomicrograph ×570.

TABLE I

DAMAGE TO THE SKIN EPITHELIUM AFTER IRRADIATION WITH 3,000 r

Animal	Days after Irradiation	Areas Affected
1	4	(No damage)
2	4	(No damage)
3	4	Head
4	6	Tail
5	7	Part of tail
6	8	Posterior part of body and tail
7	12	Separate, very limited portions
8	12	One side of head
9	13	Part of tail
10	13	Posterior portion of body
11	13	Head
12	13	(No damage)
13	13	Anterior portion of head
14	13	Anterior portion of jaws
15	13	Posterior portion of body
16	15	Anterior portion of jaws
17	15	End of tail
18	16	Tail and head
19	16	Head
20	16	Separate, very limited portions

epithelium are widely recognized as being very important in evaluating the effects of irradiation. In most instances, a reaction to radiation involves the development of giant cells and degeneration of the epithelium.

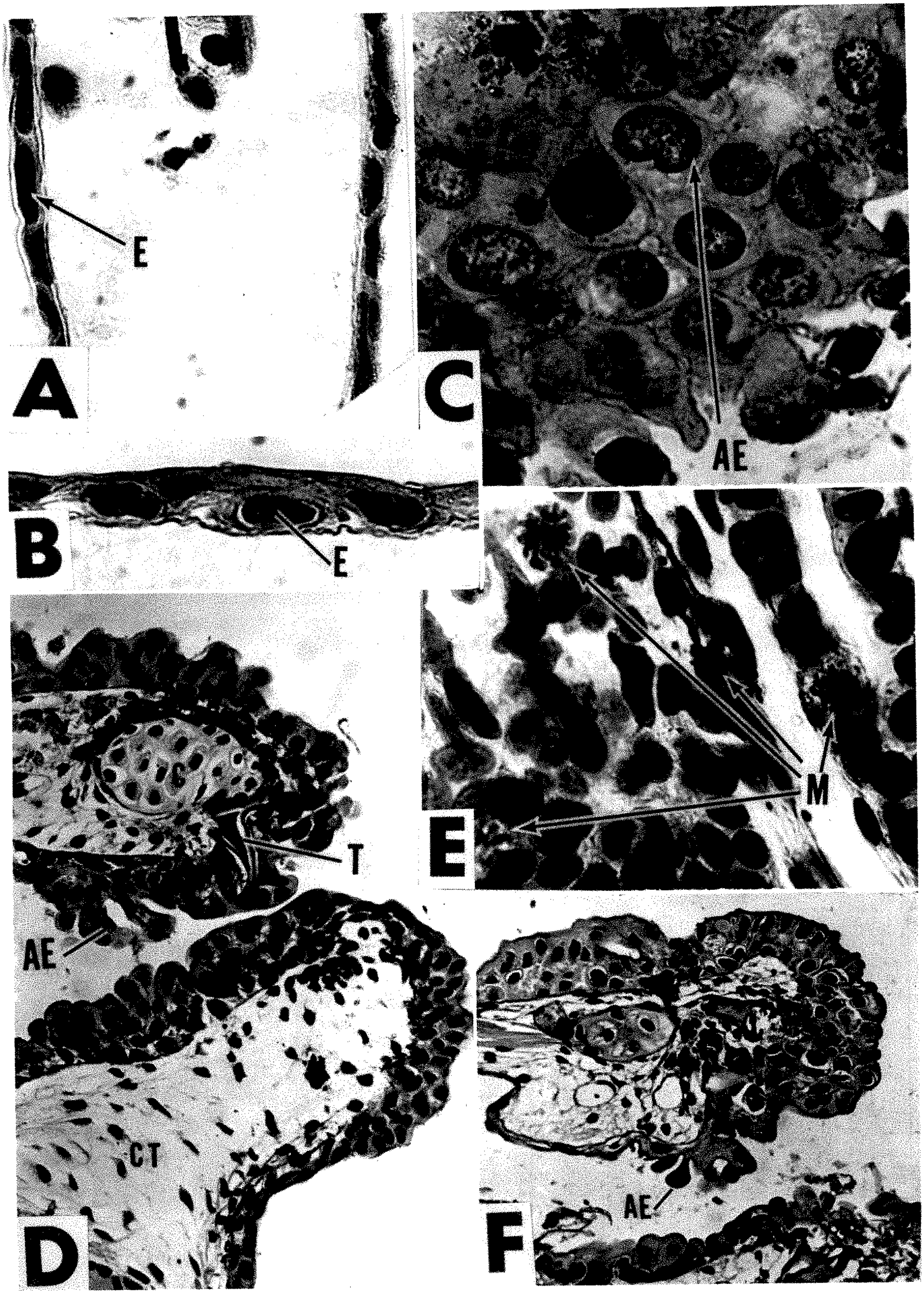
Axolotls as young as those used in the present study are highly sensitive to radiation, as was demonstrated by the definite suppression of growth and the very large mortality in this study. Under the circumstances, the response to irradiation could very reasonably be expected to be total and highly monotonous, especially after doses as large as 2,000 or 3,000 r.

Actually, however, there was no such simple response. Even after 3,000 r, the response of the skin epithelium was very diverse, and even at its most severe was only partial. Not a single animal with totally damaged skin epithelium could be found, but the skin epithelium was completely normal in some instances even after 3,000 r.

Of 20 animals examined after irradiation with 3,000 r (Table 1), the skin epithelium was completely normal in 2 animals 4 days after irradiation, and in 1 animal 13 days after irradiation. The normality of the skin epithelium in the first 2 animals is not hard to explain, since the latent period for the skin epithelium under the conditions involved was evidently greater than 4 days in these 2 animals; but the normality of the skin epithelium in the third animal is surprising, since the last animals surviving the same dose died only 3 days later.

Typical normal skin epithelium could be found in every irradiated animal, at least in some regions (Fig. 5, *B* and *D*; 6, *B*, *D* and *E*; 9 *D*; 11*E*). It was not easy to decide which areas of the skin epithelium were most sensitive to radiation, since even the areas damaged most often (the head and tail, especially the end of the tail) were completely normal in some animals re-

FIG. 5. Histology of normal and irradiated axolotls. (*A*) Part of frontal section through distal portion of tail of normal larva 33 days after hatching. E, cell of skin epithelium. Photomicrograph ×170. (*B*) Part of frontal section through tail of irradiated larva 33 days after hatching (21 days after irradiation with 1,500 r). E, nucleus of epithelial cell. Photomicrograph ×570. (*C*) Part of frontal section through tail of irradiated larva 26 days after hatching (14 days after irradiation with 2,000 r). AE, nucleus of abnormal (giant) epithelial cell. Photomicrograph ×570. (*D*) Part of sagittal section through distal portion of lower jaw of irradiated larva 24 days after hatching (12 days after irradiation with 3,000 r). AE, abnormal epithelium; CT, loose connective tissue; T, tooth anlage. Photomicrograph ×170. (*E*) Part of frontal section through body of irradiated larva 37 days after hatching (25 days after irradiation with 100 r). M, mitotic activity in connective and epithelial tissues. Photomicrograph ×570. (*F*) Part of sagittal section through distal portion of jaw of irradiated larva 40 days after hatching (28 days after irradiation with 400 r). AE, abnormal epithelium. Photomicrograph ×170.


A
E
B
E
C
AE
D
T
AE
CT
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M
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AE

ceiving the same dose (Table 1). Curiously, damage to the skin epithelium was no greater in some of the last animals surviving 3,000 r than in some other irradiated animals.

In certain instances, damage following irradiation was only slight. The nuclei of cells of the cutaneous or oral epithelium were enlarged very little, although the epithelium did develop an uneven outer surface and separate cells protruded from that outer surface in some places (Fig. 5, *D* and *F*).

True giant cells also developed. The simple squamous epithelium of the tail (Fig. 5*B*) became transformed, within 14 days after irradiation, into stratified epithelium consisting of giant cells with giant nuclei (Fig. 5*C*; 9, *E* and *F*). Even so, the resulting giant nuclei never reached the size of the giant nuclei that developed, for example, after local irradiation of the head of the young axolotl.[4]

Giant-cell epithelium is ordinarily characterized by an irregular structure and an uneven outer surface (Fig. 9, *E* and *F*). In the present study, however, the skin epithelium sometimes underwent a transformation that had never been observed before, a transformation from simple squamous epithelium (Fig. 6*B*) into stratified columnar epithelium. This latter type of epithelium generally has a basal layer of almost cuboidal cells, together with an outside layer of cells that are mostly columnar, but almost completely isolated from one another. All of the cells of the outside layer have almost the same height, and give the impression of a very precise structure (Fig. 6, *A* and *C*; 11*D*). It is interesting that this type of epithelium was observed in some places after highly different doses: small (300 r), medium (1,000 r), and large (2,000 r).

Loose Connective Tissue. After any dose of radiation used in the present study, the loose connective tissue remained normal in appearance (Fig. 6, *D* and *E*; 9*G*).

Muscle. Even in the last animal surviving irradiation with 1,500 r, muscle tissue also remained completely normal in appearance (Fig. 10*D*).

Skeletal Tissues. No changes in bone or cartilage were observed after irradiation (Fig. 5, *D* and *F*; 8, *A–C*; 11*A*).

Neural Tissue. After irradiation, the neural tissue likewise had a normal appearance (Fig. 11*C*).

Mitotic Activity. After irradiation with only 100 r, mitotic activity was normal, or perhaps even stimulated (Fig. 5*E*). After all larger doses, however, mitotic activity was obviously suppressed.

HISTOPATHOLOGY OF IRRADIATED ORGANS

Intestinal Tract. Pathologic changes in the intestinal tract were not observed. The epithelium of the stomach and intestines appeared normal (Fig. 9, *A* and *B*; 10*B*).

Liver. Variations in the size of the nuclei of liver cells were extensive after irradiation; but they did not exceed the range of such variations in normal animals, and hence the liver can presumably be considered to have remained normal after irradiation (Fig. 4*C*; 10*C*).

Spleen. Damage to the spleen in irradiated animals was obvious. Only after irradiation with a dose as small as 100 r was the spleen ever apparently normal (Fig. 7*A*). After larger doses, however, the spleen always became greatly reduced in size (Fig. 7, *B–D*), especially in the last animals surviving large doses (Fig. 9*C*; 11*B*). After irradiation, the number of cells in the spleen was also greatly reduced. It is clear that irradiation was followed by degeneration of the spleen. Such degeneration was characterized by the presence of pigment cells and large cells with granulated cytoplasm in the spleen (Fig. 7, *C* and *D*; 9*C*).

Blood Vessels and Blood Cells. In all irradiated animals, the number and sizes of blood vessels and the number of blood cells obviously underwent a major diminution.

Olfactory Chambers. In all irradiated animals, even in the last animals surviving 2,000 r, the olfactory chambers remained normal (Fig. 11*C*).

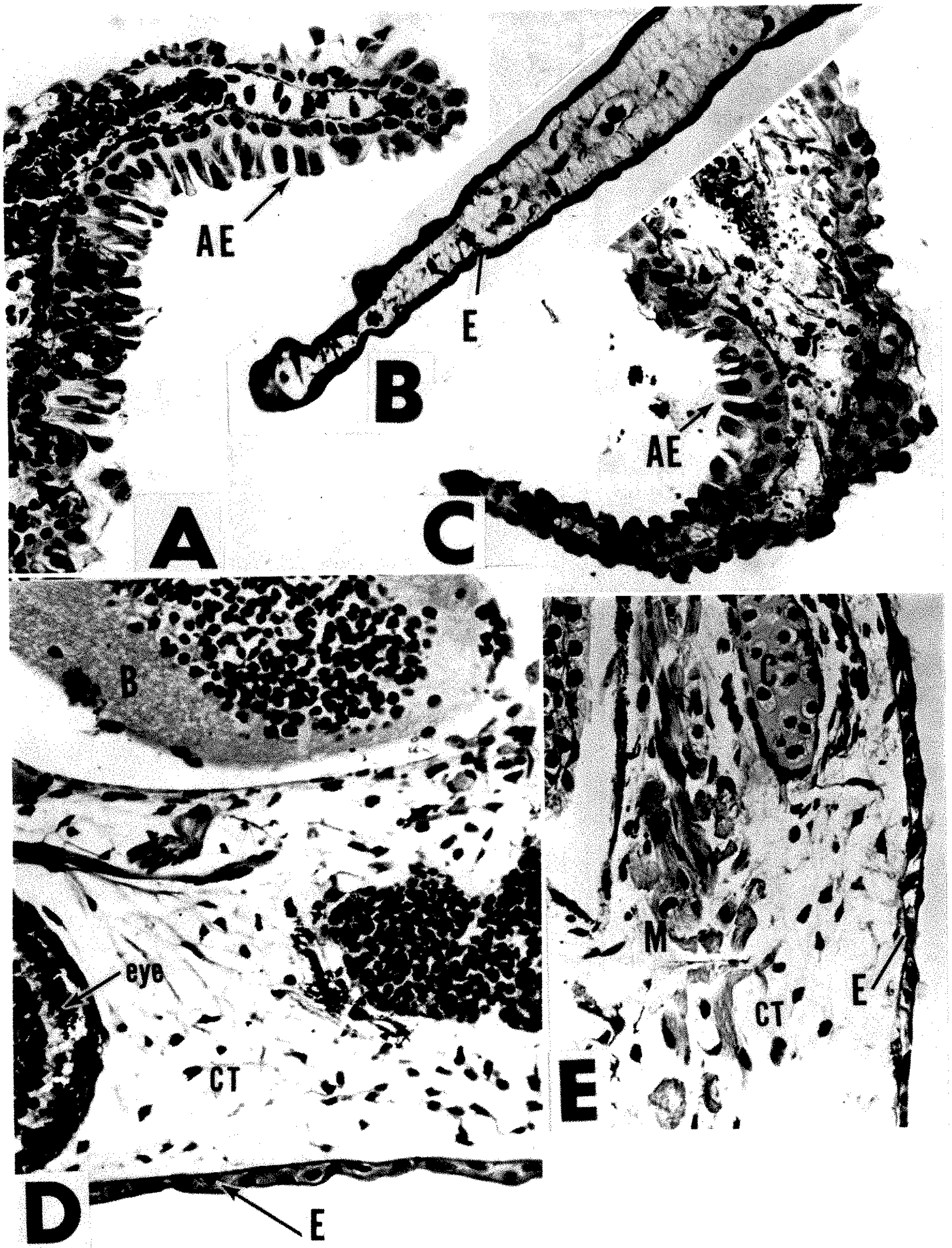

FIG. 6. Histology of irradiated axolotls. (*A*) Part of frontal section through distal portion of tail of irradiated larva 43 days after hatching (31 days after irradiation with 300 r). AE, abnormal skin epithelium. Photomicrograph ×170. (*B*) Part of frontal section through distal portion of tail of irradiated larva 34 days after hatching (22 days after irradiation with 400 r). E, normal skin epithelium. Photomicrograph ×170. (*C*) Part of frontal section through distal portion of tail of irradiated larva 26 days after hatching (14 days after irradiation with 1,000 r). AE, abnormal skin epithelium. Photomicrograph ×170. (*D*) Part of frontal section through head of irradiated larva 29 days after hatching (17 days after irradiation with 600 r). B, brain; CT, connective tissue; E, skin epithelium. Photomicrograph ×170. (*E*) Part of frontal section through head of larva 30 days after hatching (14 days after irradiation with 1,000 r). C, cartilage; CT, connective tissue; E, normal skin epithelium; M, muscle. Photomicrograph ×170.

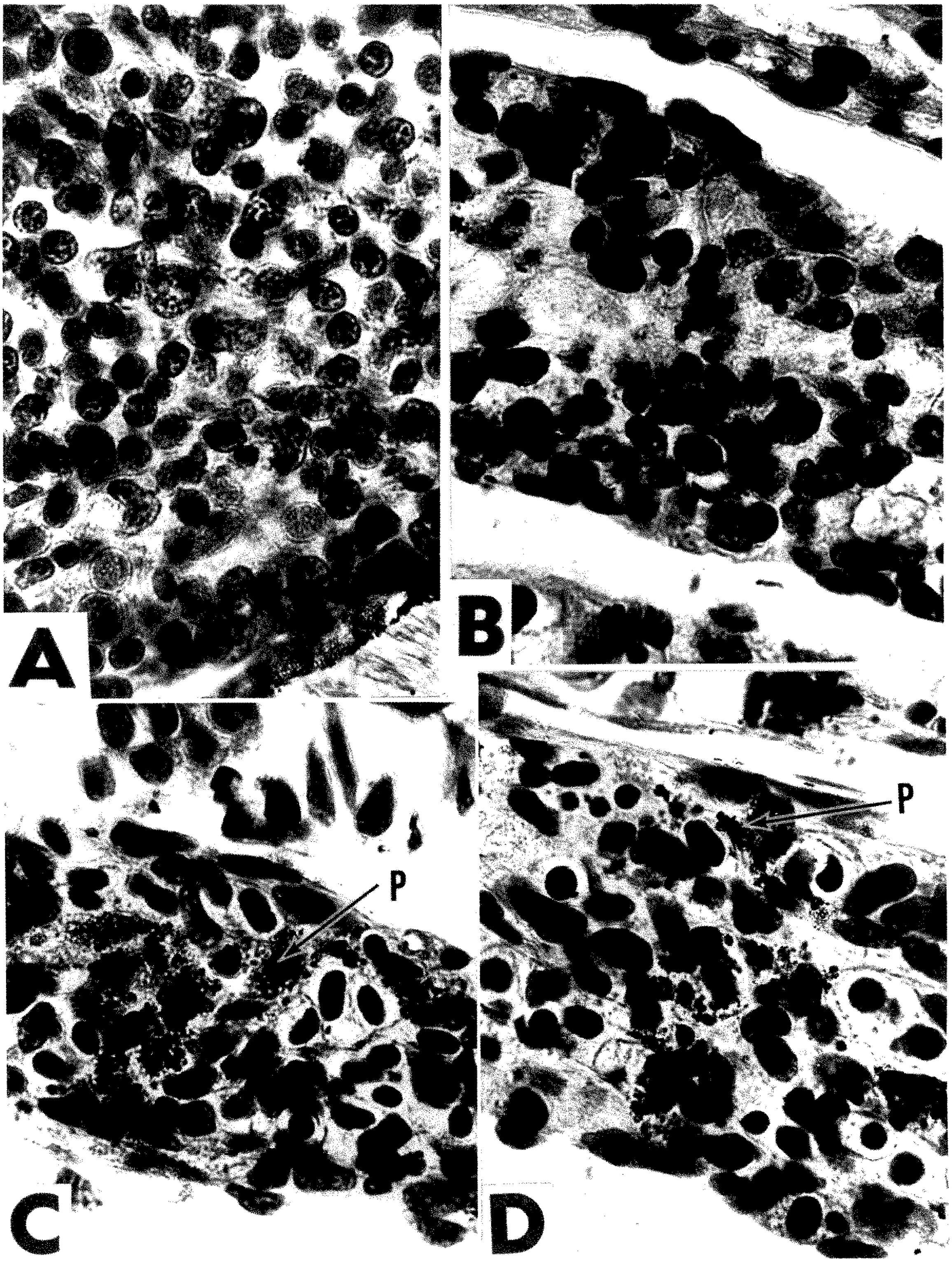

FIG. 7. Normal and damaged spleens. (*A*) Part of section through normal spleen of irradiated larva 76 days after hatching (64 days after irradiation with 100 r). Photomicrograph ×570. (*B*) Part of section through spleen or irradiated larva 33 days after hatching (17 days after irradiation with 600 r). Photomicrograph ×570. (*C* and *D*) Portions of sections through spleens of two larvae 31 days after hatching (15 days after irradiation with 1,500 r[*C*] or 3,000 r [*D*]). P, cells with pigment and granules. Photomicrographs ×570.

Eyes. In all irradiated animals, the eyes were completely normal, except for slightly retarded development (Fig. 8, *A–D*; 10*A*; 11*A*), even in the last animals surviving 2,000 and 3,000 r (Fig. 11*A*). Special attention should be given to the animal shown in Figure 8*C*. This animal was irradiated with 3,000 r. The last animals surviving this dose died 19 days after irradiation, but this animal was fixed 18 days after irradiation. Portions of the eye as radiosensitive as the rod-and-cone layer and the cornea were completely normal in this animal, as the Figure shows.

DISCUSSION

The findings obtained in the present study lead to the paradoxical conclusion that observable changes in the tissues can be extremely small even in the last animals surviving a dose as large as 2,000 r (Fig. 9, 10 and 11), in spite of the generally lethal effect of all doses from 100 r up and the definitely lethal effect of all doses above 200 r. Presumably the reason why the animals died was that irradiation was followed by complete degeneration of the spleen. The effect on the spleen is considerably more important in these animals than it would otherwise be, since they lack bone marrow, and the lymph nodes and the lymphoid tissue in the peripheral portion of the liver do not develop until much later, about 1½ months after hatching. In fact, the spleen is probably the only blood-forming organ that these animals have at this early stage in their development. That being the case, the immediate cause of death for the animals dying as a result of irradiation was most likely exhaustion of the blood following disappearance of the blood cells. Damage to the skin epithelium was comparatively limited, and would seem to be of little or no importance in relation to the lethal effect of radiation.

All other tissues and organs in the irradiated animals appeared normal. Even such highly radiosensitive organs as the olfactory chambers and the eyes, especially the cornea, the rod-and-cone layer, and the lens, appeared normal even in the last animals surviving the largest doses. Why did most tissues and organs appear normal? Paradoxically, the regions without directly observable damage appeared normal because the animals died as quickly as they did, before the latent periods for these particular tissues and organs were completed. The latent period for each region of an organism is independent of the general condition of the organism. Even if the organism is sick from the effects of radiation, even if it is dying from those effects, a tissue whose latent period has not been completed will appear normal. Irradiation damage to the tissues can be much greater if the animals are older at the time of treatment, and hence less sensitive and thus able to survive the effects of radiation for a much longer period.

The length of the latent period depends upon the amount of radiation administered. By administration of a very high dose, the latent period can be largely or completely eliminated. Gerstner, Lewis, and Richey[11] found immediate and complete abolition of function, together with morphologic changes, in isolated striated frog muscle irradiated with 150,000 r. Severe histologic alterations in rabbit muscles were seen 24 hours after irradiation. In the mucoid cells of male albino mice, the diameter of the secretory granules was increased by approximately 80 per cent 24 hours after irradiation.[13]

Some organisms are extremely radiosensitive, and hence a response to radiation can be observed very early, even after only a moderate dose. According to Vogel,[21] marked pathologic changes in the retina in newborn mice can be observed 3 to 4 hours after irradiation with as little as 1,000 r. Brace, Andrews, and Thompson[2] observed that a characteristic tetanic state developed in guinea pigs less than an hour after irradiation with 10,000 to 25,000 r, and persisted until the animals were moribund.

If the dose is high enough, death may occur "under the beam." Henshaw[14] gave

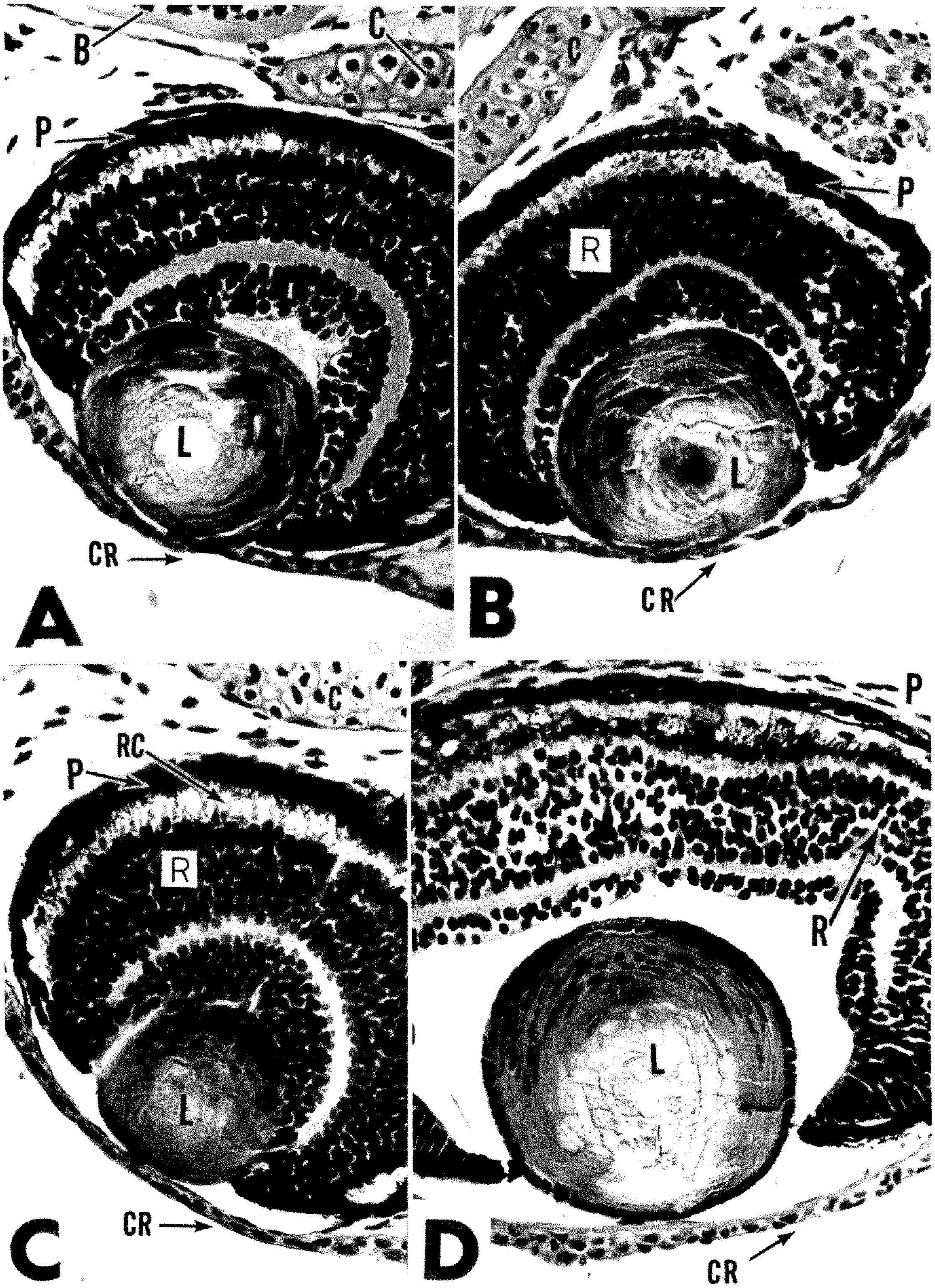

FIG. 8. Eyes of irradiated and control animals. (*A*) Part of section through eye of irradiated larva 22 days after hatching (10 days after irradiation with 2,000 r). B, brain; C, cartilage; CR, cornea; L, lens; P, pigment layer. Photomicrograph ×170. (*B* and *C*) Portions of sections through eyes of two larvae 30 days after hatching (18 days after irradiation with 2,000 r [*B*] or 3,000 r [*C*]). C, cartilage; CR, cornea; L, lens; P, pigment layer; R, retina; RC, rod-and-cone layer. Photomicrographs ×170. (*D*) Part of section through eye of control larva 40 days after hatching. CR, cornea; L, lens; R, retina; P, pigment layer. Photomicrograph ×170.

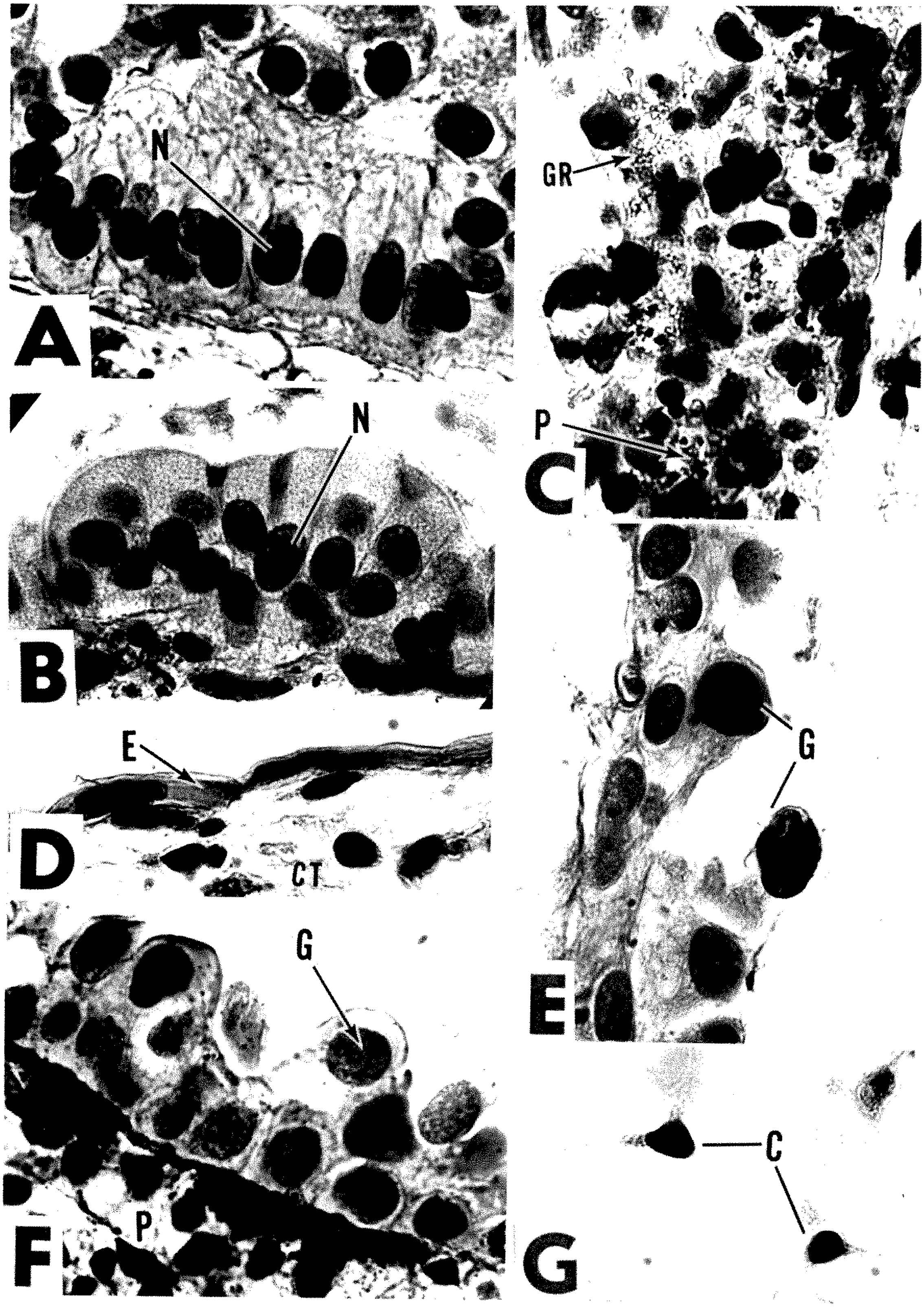

FIG. 9. Portions of sections through tissues and organs of last surviving irradiated animals 34 days after hatching (22 days after irradiation with 1,500 r). All photomicrographs ×570. (*A*) Epithelium of stomach. N, nucleus. (*B*) Epithelium of intestine. N, nucleus. (*C*) Spleen. Gr, cells with granules; P, cells with pigment. (*D-F*) Normal (*D*) and giant-cell (*E* and *F*) skin epithelium. E, epithelial cells; CT, loose connective tissues; G, giant nuclei; P, pigment cells. (*G*) Connective tissue cells, C.

doses of 50,000 r to mice, rabbits, and guinea pigs, and the animals usually died during exposure. Severe morphologic changes occurred in hamsters that died during exposure to 110,000 r.[19] Temporary inhibition of mitotic activity can be observed 1 hour after irradiation with a very small dose, such as 64 r in the case of grasshopper neuroblasts.[10] Frog tadpoles can be killed in a period of $1\frac{1}{2}$ hours through the use of 160,000 r of roentgen rays.[18] Glocker and Langendorff[12] showed that frog eggs did not continue cleavage after roentgen irradiation with 600,000 r; *i.e.*, the latent period was absent, and the reaction took place immediately.

It must be recognized that some variation in the length of the latent period is possible for animals of the same species and the same age. Likewise, variation in sensitivity to radiation also occurs in animals of the same species and the same age. Latent period and radiosensitivity are not constants.

Differences of several days in the length of the latent period can be observed even in animals of the same age. In a previous study,[6] the effects of radiation on the cornea in axolotls of exactly the same age as those in the present study were somewhat different. In the present study, the cornea was completely normal 18 days after irradiation with 3,000 r. In the previous study, however, the cornea had undergone significant changes only 17 days after irradiation with the same dose: the cells of the corneal epithelium were increased in size but decreased in number, and melanophores were present among the epithelial cells. Complete disorganization of the corneal epithelium took place in 21 days. In the present study, the last animals surviving irradiation with 3,000 r died 19 days after irradiation, presumably very close to the end of the latent period for the cornea. Only one or two more days of survival, and damage to the cornea would most likely have become evident. In any case, it is interesting that radiation damage occurred slightly earlier in the previous study, in view of the fact that irradiation was local in the previous study but total-body in the present one.

Even after irradiation with 4,000 r, the latent period for the cornea, lens, and retina is much longer in 1 year old axolotls.[9] The same thing is true in the adult animals.[7]

In the young axolotl, the olfactory epithelium is one of the most radiosensitive of all areas of the head, and truly normal olfactory epithelium was never found after irradiation in a previous study.[4] "However, in 17 per cent of the cases . . . , the epithelium of the olfactory chambers was only slightly damaged. The typical orientation of olfactory cells disappeared. It is necessary to take into consideration that, with one exception, such slightly damaged olfactory epithelium was discovered only after early fixation (between 13 and 36 days post-irradiation). From this we can conclude that the olfactory epithelium reacts with comparative slowness to irradiation."

In that previous study,[4] axolotls were irradiated with 3,000 or 6,000 r 25 or 32 days after hatching, and only the anterior portion of the head was exposed. In the present study, the animals were much younger, but no damage developed in the olfactory chambers. Obviously the radiosensitivity of the olfactory chambers was different at the different ages represented in the two studies, but the difference in the radiosensitivity was opposite to what would be expected in view of the fact that the olfactory chambers are highly radioresistant in adult animals, but highly radiosensitive in young animals. In adult axolotls, normal olfactory epithelium was still present in some areas even after irradiation with 10,000 r; complete disappearance of the olfactory epithelium and its replacement with skin epithelium following irradiation was often observed in young animals,[4] but never in adult animals.[8]

In the skin epithelium of axolotls irradiated 14 days after hatching,[5] the first changes were noted 8 days after 8,000 r, 14 days after 6,000 r, 17 days after 3,000 r, 21 days after 1,000 r, and 25 days after 500 r. These findings are closely comparable to

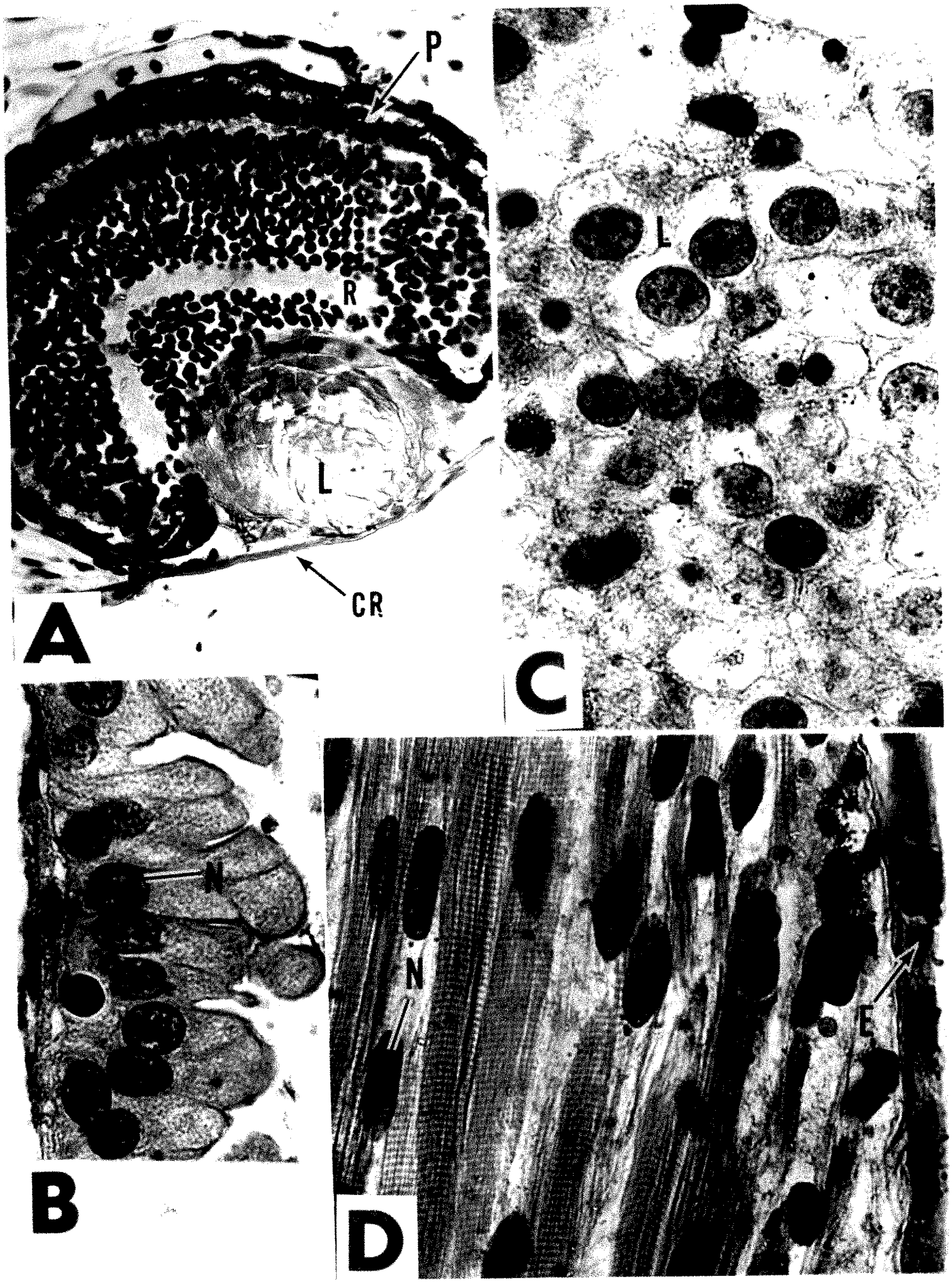

FIG. 10. Portions of sections through tissues and organs of last surviving irradiated animal 34 days after hatching (22 days after irradiation with 1,500 r). (Continuation of Fig. 9.) Photomicrographs ×570, except where otherwise noted. (*A*) Eye. CR, cornea; L, lens; P, pigment layer; R, retina. Photomicrograph ×170. (*B*) Intestinal epithelium. N, nucleus. (*C*) Liver. L, liver cell. (*D*) Muscle and skin epithelium. N, nucleus of muscle cell; E, skin epithelium.

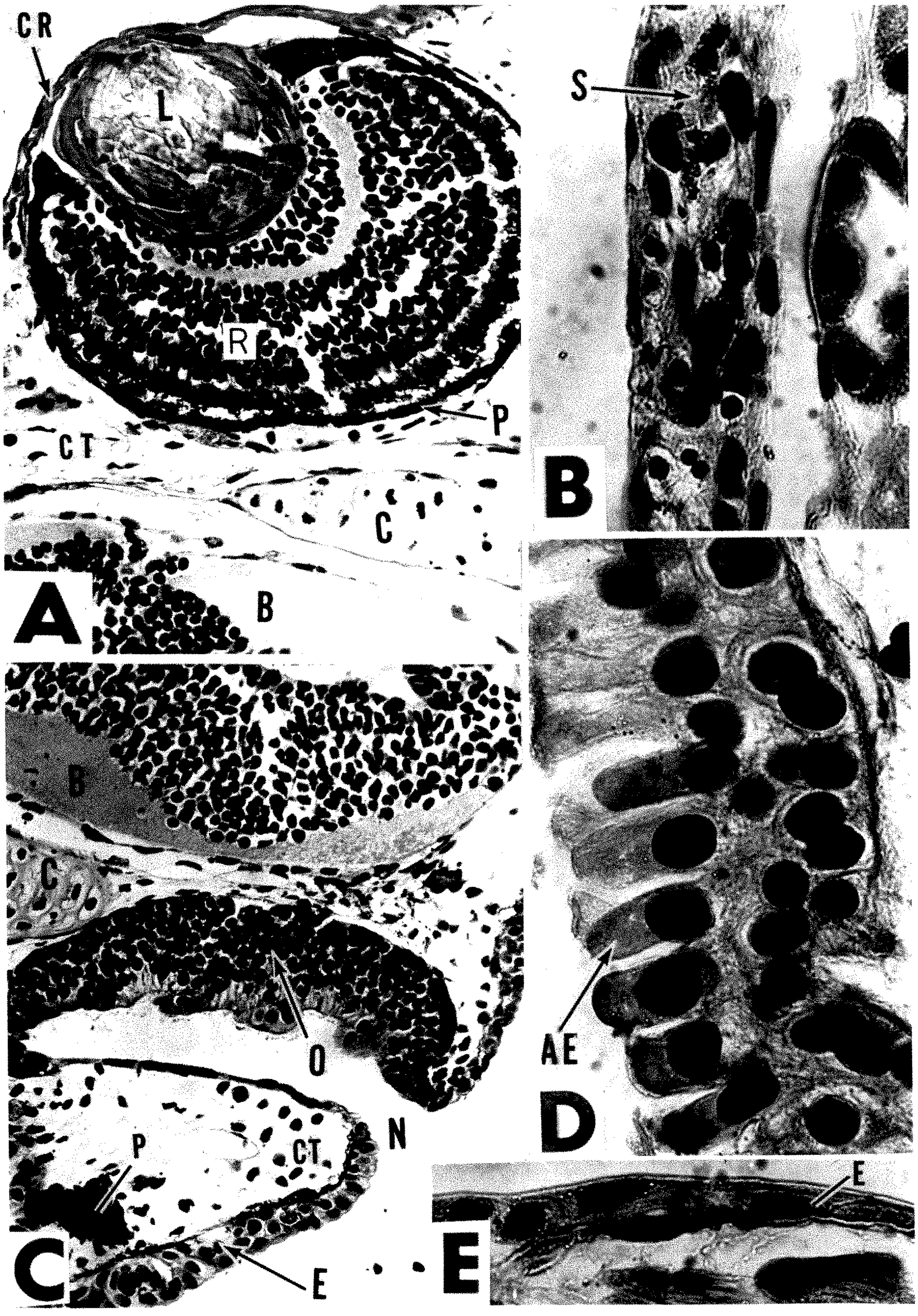

FIG. 11. Portions of sections through tissues and organs of last surviving animal 35 days after hatching (23 days after irradiation with 2,000 r). Photomicrographs ×570, except where otherwise noted. (*A*) Eye. B, brain; C, cartilage; CR, cornea; CT, connective tissue; L, lens; P, pigment layer; R, retina. Photomicrograph ×170. (*B*) Spleen, S. (*C*) Brain and olfactory chamber. B, brain; C, cartilage; CT, connective tissue; E, skin epithelium; N, nostril; O, olfactory epithelium; P, pigment cell. Photomicrograph ×170. (*D* and *E*) Abnormal (*D*) and normal (*E*) skin epithelium. AE, abnormal epithelial cell; E, normal epithelial cell.

those obtained in the present study.

Evidently radiation damage is not always visible. That being the case, the differences between "visible changes in cells" and "invisible changes" are real, and not merely apparent.[1] Total-body irradiation is very often followed by only partial damage to tissues and organs. In the present study, this was the case in the cutaneous and oral epithelium.

In a previous study,[3] axolotls were irradiated with 3,000 r 30 days after hatching, or with 6,000 r 47 days after hatching. After 3,000 r, the number of cells in the spleen was greatly reduced, and a limited number of usually large cells with granulated protoplasm were observed. These findings were essentially the same as those obtained in the present study. After 6,000 r, however, the spleen was sometimes much larger than normal. In such a spleen, there was extensive mitotic activity, even though the animal was severely injured and was dying from radiation damage. This unusual mitotic activity can be considered an instance of roentgen stimulation. Only in rare cases is the combination of dose and age—here 6,000 r 47 days after hatching—exactly right to produce this effect. The situation can be compared to that of the type of master key that opens a small number of different locks, but not any others. Thus radiation stimulation can be observed only in rare cases.

SUMMARY

The present study utilized 650 axolotls (*Siredon mexicanum*), 12 days after hatching. In one series of experiments involving 500 animals from one spawning, nine groups of 50 animals each received total-body irradiation with 200, 300, 400, 600, 800, 1,000, 1,500, 2,000, and 3,000 r, respectively. In another series of experiments involving 150 animals from another spawning, two groups of 50 animals each received 100 and 200 r, respectively. In each series of experiments, the remaining 50 animals served as untreated controls.

1. All doses from 200 r up very definitely suppressed growth.

2. The response of the skin epithelium to irradiation, even with a dose as large as 3,000 r, was highly diverse, and at most only partial. Not a single animal with totally damaged skin epithelium could be found, but the skin epithelium was completely normal in some instances even after 3,000 r. In some areas of the skin epithelium of irradiated animals, giant cells developed and the simple squamous epithelium was transformed into stratified columnar epithelium.

3. Loose connective tissue, muscle, skeletal tissues, and neural tissue were completely normal in all irradiated animals.

4. Likewise, the intestinal track, the liver, the olfactory chambers, and the eyes were completely normal in all irradiated animals.

5. Damage to the spleen in irradiated animals was obvious. The organ was greatly reduced in size, and the number of cells in it was also greatly reduced. The presence of pigment cells and large cells with granulated cytoplasm was characteristic of the degenerated spleen.

6. The number and size of blood vessels and the number of blood cells was obviously reduced.

7. Mitotic activity was greatly suppressed.

8. Paradoxically, visible changes in the tissues were extremely limited, despite the decidedly lethal effect of even small doses of radiation. Presumably the reason why the animals died was that irradiation was followed by complete degeneration of the spleen. It seems that the spleen is the only blood-forming organ that these animals have at this early stage in their development, and hence the immediate cause of death for the irradiated animals was probably exhaustion of the blood as a result of disappearance of the blood cells.

9. Even such radiosensitive organs as the olfactory chambers and the eyes were normal in irradiated animals. Paradoxically, the regions without directly observable damage appeared normal because the animals died as quickly as they did, before the latent periods for these particular tissues

and organs were completed. The latent period for each region of an organism is independent of the general condition of the organism. Even if the organism is sick from the effects of radiation, even if it is dying from those effects, a tissue whose latent period has not been completed will appear normal.

10. It must be recognized that some variation in the length of the latent period is possible for animals of the same species and the same age. Likewise, variation in sensitivity to radiation also occurs in animals of the same species and the same age. Differences of several days in the length of the latent period can be observed even in animals of the same age.

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THE RELATIVE BIOLOGIC EFFECTIVENESS OF COBALT 60 GAMMA AND 200 KV. X RADIATION FOR CATARACT INDUCTION

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THE purpose of the present study was to compare the biologic effectiveness of x radiation produced at 200 kvp. and the gamma radiation of cobalt 60. The biologic criterion was the induction of radiation cataract in the rat lens.

The response of the mammalian lens to ionizing radiation by the induction of cataract is well known. The related factors of dose, time of onset, time-dose relationship and other similar aspects of the problem have been described in the publications of such workers as von Sallmann *et al.*,[24] Cogan *et al.*,[2,3] Leinfelder and Kerr,[9] Riley *et al.*,[14–16] Upton *et al.*,[20,22,23] and Merriam and Focht and their co-workers.[4,11–13]

A study and a summary of relative biologic effects (RBE) in mammalian systems has been prepared by Storer *et al.*[19] For the production of 30 day lethality and testicular atrophy in mice, the RBE reported was 0.77 for cobalt 60 gamma rays compared to 250 kv. x radiation at a half value layer of about 2.5 mm. of Cu. For splenic and thymic atrophy in the mouse, the RBE was unity. Berg and Lindgren[1] found cobalt 60 radiation less effective than 200 kv. x rays at a half value layer of 0.9 mm. Cu for brain damage in rabbits. More recently, Hall[5] has compiled data from the literature. The only figure he found for cobalt 60 radiation was that by Upton *et al.*[21] of 0.7 compared to x radiation produced at 250 kv. for lethality in mice. For the effect on broad bean roots within a water phantom, Hall obtained 0.84 for cobalt 60 gamma rays compared to 220 kv. x rays. An experiment by Crabtree, also summarized by Hall, reported an RBE of 1 between radium gamma rays and 200 kv. x radiation for the reduction in glycolysis in the rat retina.

Sinclair *et al.*,[17,18] using the LD_{50} for the mouse, rat, chick embryo and yeast, and Fe^{59} uptake in rats, found RBE values of 0.82 to 0.93 for cobalt 60 radiation compared to 200 kv. x rays. Loken *et al.*[10] obtained an RBE of 0.81 for the effect of cobalt 60 gamma rays compared to x rays in inhibiting the hatching of chicken eggs. In a recent analysis, Krohmer[8] found an RBE for cobalt 60 radiation with respect to x radiation to be 0.90 for survival of HeLa cells. The x rays ranged from 100 kvp. and a half value layer of 5.0 mm. Al to 250 kvp. and a half value layer of 3.2 mm. Cu.

Upton *et al.*[22] published some results which would give an RBE of about 0.8 for the gamma radiation from cobalt 60 compared to 250 kv. x radiation for induction of lens opacities in mice and rats. These were whole body irradiations and the question of systemic effects and selection due to observing only survivors may arise.

From the literature it would appear that an RBE of 0.7 to 1.0 has been found for cobalt 60 gamma compared to 200 kv. x radiation. Little work has been done using the mammalian lens as the indicator and it was felt that further studies utilizing large groups of animals to give results of greater statistical significance would be valuable.

The rat lens should be a good biologic in-

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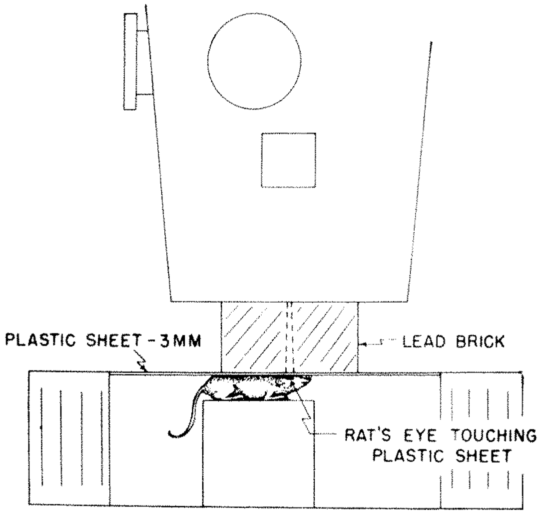

Fig. 1. The experimental set-up for the cobalt 60 unit. The machine shutters defined a field of about 3 cm.×3 cm. on the surface of the lead brick. The opening in the latter was 1.6 cm. on the exit side, at 30 cm. distance.

dex for several reasons. It is part of a mammalian system and thus may have more clinical significance than organisms in other classes. Since the lens is a small volume near the surface, it is readily accessible for accurate radiation dosimetry, and can be irradiated without complications due to effects on other tissues. The dose and the radiation quality can be determined without significant corrections for such effects as absorption or scatter. The spatial distribution of dose over its small volume will be very nearly the same for most energies of radiation.

EXPERIMENTAL ANIMALS

Adult female rats of the White Sherman strain were used. Their age was chosen at about 4 months so that the life span would be long, and so that the question of increased sensitivity of the very young lens would be eliminated. Groups of 6 or less were kept to a cage, with food and water *ad libitum*. They were anesthetized at the time of irradiation with a subcutaneous injection of sodium pentobarbital according to body weight. Thereafter they were handled only for eye examinations and for cage cleaning, and were housed in the regular animal room.

RADIATION FACTORS AND DOSIMETRY

The standard radiation was an x ray beam produced at 200 kvp. and filtered by 0.5 mm. of copper, giving a half value layer of 1.0 mm. of copper. A 16 mm. field irradiated one eye only, with whole body protection for the x radiation as described in previous papers.[4,12]

For the cobalt 60 irradiation, the set-up was as in Figure 1. A lead brick 5 cm. thick with a circular hole, tapered to fit the beam at the treatment distance, defined the field. A 3 mm. layer of plastic absorbed any secondary electrons emitted from the lead surface and provided enough low atomic number material in the path of the beam to achieve electronic equilibrium. Suitable material under the rat's jaw and body provided a constant amount of back scatter.

X ray dosimetry was studied in a phantom mock-up using a small Baldwin-Farmer ionization chamber and film isodoses as described in an earlier paper.[4] In the present work, similar film isodoses were measured with the cobalt 60 unit. The irradiated area was at least 8.5 mm. wide at the 99 per cent isodose, and 10 mm. wide at 98 per cent isodose. A factor for the chamber for cobalt 60 radiation was obtained by comparison with a 25 r Victoreen high energy chamber calibrated at the Bureau of Standards. Stem effects were checked for both chambers, with and without the stem shielded, and no differences were found within 1 per cent.

Depth dose curves in terms of surface dose as 100 per cent were drawn from data in the literature for the small field sizes and for the target skin distances of 23 cm. for the x ray set-up and 30 cm. for the cobalt 60 set-up. From a histologic section of one of the rat's eyes, the anterior portion of the lens was estimated to be 1 mm. below the surface, and the anteroposterior diameter of the lens was 3 mm. A point on its anterior surface would, from the x ray depth dose curve, get about 3.5 per cent

greater dose than the center, and a point on its posterior surface would receive about 2.5 per cent less. The cobalt 60 curve showed somewhat less of a change across the anteroposterior dimension, the variation being about plus or minus 2 per cent of the value at the center.

The axis of the small chamber was placed perpendicular to the axis of the beam. Its diameter of 4 mm. was in the anteroposterior direction of the lens. It occupied approximately the volume and position of the latter and read an average value of the radiation distribution throughout it.

For the cobalt 60 set-up the chamber just touched the underside of the plastic. In order to test the decrease of radiation along the axis of the beam, two plastic caps were made to fit the Baldwin-Farmer chamber snugly. The first had a wall thickness of 1 mm., and the second of 2 mm. Using these in succession, the chamber was moved down through the phantom to two corresponding distances. Within this 2 mm. there was no decrease detectable within 1 per cent despite estimates from data in the literature as above. It was concluded, therefore that the dose distribution through this dimension of the lens was more uniform than expected.

METHOD OF TREATMENT

Alternate eyes of successive animals were irradiated; thus one rat had the right eye exposed and the next the left. In each animal only one eye was treated and the other served as a control. At subsequent examinations the observer did not know which eye had been irradiated or which group was being examined. Groups of 25 to 30 rats were used for each different quality or amount of radiation. Each animal was identified by an ear punch coding system.

Measurements of the dose were made originally in units of roentgens, since this was easier to use due to usual calibration methods, and due to the impermanence of the conversion factor at that date. The factor for conversion for cobalt 60 gamma rays taken from Handbook 87[7] is 0.96 rads per r for muscle or water. For x radiation of half value layer of 1.0 mm. Cu, the factor from Handbook 78[6] is 0.95 rads per r for muscle. In all cases the rat's eye was at the surface of a small field so that the spectral distribution of the radiation had not been changed sufficiently by scattering within the tissue to require corrections of the factors from the above values.

Since the main question is not the absolute dose, but the relative effect of the radiations, and since there is only about 1 per cent difference in the absorbed dose, the numerical values of the r exposures have been relabeled as rads.

Different groups of animals were given doses of 2,000, 1,500, 1,000 and 500 rads of x radiation in a single treatment. Divided doses of the same totals were given to other groups with 1/3 of the total given on the first, third, and sixth days. For each group the treatment time extended over a period of about 7 hours. In the fractionation studies, the animals, which were individually identified, were treated in the same order each time, so that the time interval between treatments for each would be approximately the same.

In this RBE investigation, single and divided doses of 1,500 rads of cobalt 60 radiation were given. The dose rate for the lens was about 180 rads per minute for the x radiation, and 130 rads per minute for the cobalt 60 beam. With the x ray machine the radiation was delivered at a rate of 60 pulses per second, due to the half wave rectification. In the case of the radioisotope it was continuous.

SCORING

Each eye of every animal was examined with a slit-lamp (corneal microscope) before treatment and every few weeks thereafter. Each cataract was graded 0, 1+, 2+, 3+, 4+ according to increasing degrees of severity, as described in previous work.[4,12,13] During the period of observation, which extended beyond 70 weeks for the group given 1,500 rads in divided doses, only a few of the control eyes developed any senile

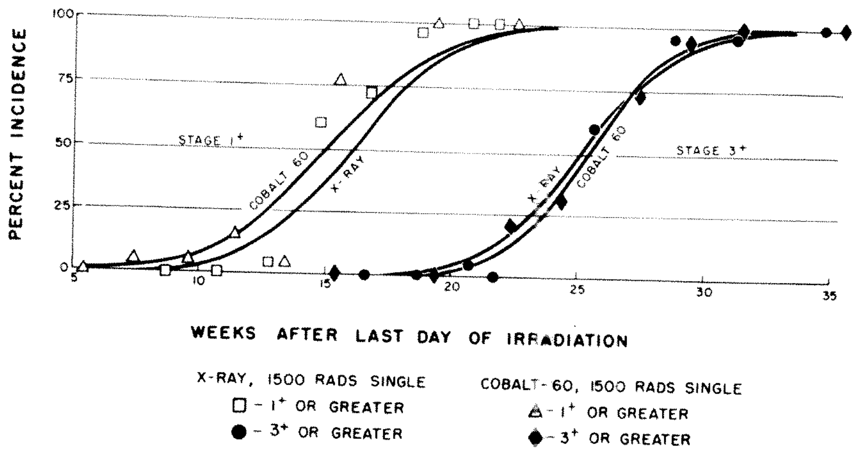

Fig. 2. Comparisons of the two groups exposed to x and cobalt 60 radiations are shown for two successive stages. There is no significant difference between the groups at either stage.

opacities, and these were toward the end of the experiment. Any rat with such a senile cataract was removed from the series when this opacity developed.

ANALYSIS OF DATA

Consideration of the data on the basis of each stage of cataract separately or on an "average" basis has been discussed in an earlier publication.[4] In the first, or quantal, analysis the percentage of animals which had reached each given stage or higher stages were plotted against the time in weeks after the last day of treatment. A few such curves are drawn in Figure 2 for both x ray and cobalt 60. Each curve is the result of a probit analysis of the data points which was done with the aid of a computer program. There was no significant difference between the two qualities for the stages shown.

The single x ray dose of 1,500 rads was repeated after an interval of 1 year to determine its reproducibility. In the first experiment male rats were used, but there is no known reason to expect a difference on the basis of sex. For this portion of the experiment, done in 1959, there was no significant difference demonstrated from the 1960 experiment.

Similar analyses, by stage, were made for the single and divided x irradiations of 2,000, 1,000 and 500 rads. Using the results for 2+ and higher, the doses were plotted against the time at which 50 per cent of the animals had reached this stage for both single and divided treatments.[4] These two isoeffect curves showed times of onset which varied fairly rapidly with the dose. Thus the effect of reasonable changes in the dose could be demonstrated by associated changes in the times of onset.

If this were not true, an RBE effect could, of course, be masked. For instance, if the time of onset of the 2+ for 1,000 rads were very near the time for 1,500 rads, a difference in the effect of the cobalt 60 gamma radiation corresponding to a change of a few hundred rads in x radiation might not be apparent. For the cobalt 60 beam, 1,500 rads, single and also divided, were the only doses used. Reports in the literature[17] have shown the biologic effects to be about as sensitive to change in dose for cobalt 60 gamma radiation as for x radiation at this dose level. The Appendix in the present report describes an arithmetical analysis of these isoeffect curves.

Lower doses of 360 rads of the x radiation were given in single and divided doses. However, the incidence of 2+ cataract was too low to be used in the above isoeffect curves. Eight of 23 animals developed 1+ or greater cataracts in 49 weeks; 2 of these were 2+ and none was more advanced. In the divided group only 1 of 18 animals developed a 1+ or greater opacity in this time. Observations after this date were not

used because of the appearance of senile lens changes. In a group given 100 rads in a single dose, no radiation cataracts appeared before the incidence of senile changes, at 95 weeks.

It would appear therefore that a single dose of 360 rads is definitely cataractogenic for this species. Dividing the treatment definitely lowered the incidence. A dose in the range of 100 rads did not result in significant lens opacities.

RESULTS

The results in terms of the number of weeks at which 50 per cent of the animals were at, or higher than, each of 4 given stages, are shown in Tables I and II. Table I compares the results of the probit analysis for the single treatments of x and cobalt 60 irradiation. The 95 per cent fiducial limits overlap very decidedly for these qualities of radiation, especially for the 3+ stage. There is thus no significant difference between the two energies of radiation at the 1+, 3+ or 4+ stages.

For the 1959 x ray group there were good data, on this basis of separate stages, only for the 2+ category. This does overlap the cobalt 60, while the 1960 group just misses overlapping, in a direction which would give an RBE greater than 1. From these results there cannot be said to be, in general, any significant difference between the two modalities of radiation.

Table II gives results of corresponding processing of the data for divided irradiations. Here the onset of the biologic injury was slower. It had not been decided to use the separate stage method of analysis at the time and there are not always enough observation points to give good curves at each cataract grade separately. For the Grade of 1+ or over, the x ray group reaches the 50 per cent value earlier. There were not enough data to give a good curve at Grade 2+ for the cobalt 60. For the Grade 3+ the cobalt 60 reaches the 50 per cent value earlier, the opposite of the Grade 1+ result. For Grade 4+ the limits overlap. From these results also, no general difference between the two energies

Table I

RESULTS OF PROBIT ANALYSIS, SEPARATE CATARACT STAGES, SINGLE TREATMENT, 1,500 RADS

Per Cent of 1+ or Greater Cataract

	X ray (1960)	Cobalt 60
Weeks for 50%	15.9	14.7
95% Fiducial Limits (weeks)	14.9–17.7	13.9–15.5
Chi Square Degrees of Freedom	8.2 (6)	13.7 (7)
Probability	>0.2	>0.05

Per Cent of 2+ or Greater Cataract

	X ray (1959)	X ray (1960)	Cobalt 60
Weeks for 50%	20.7	20.7	19.1
95% Fiducial Limits (weeks)	19.7–21.3	20.1–21.5	18.3–19.9
Chi Square Degrees of Freedom	9.8 (11)	8.1 (5)	0.3 (4)
Probability	>0.5	>0.1	>0.98

Per Cent of 3+ or Greater Cataract

	X ray (1960)	Cobalt 60
Weeks for 50%	25.2	25.3
95% Fiducial Limits (weeks)	24.5–25.9	24.4–26.2
Chi Square Degrees of Freedom	4.65 (7)	1.7 (6)
Probability	>0.7	>0.9

Per Cent of 4+ or Greater Cataract

	X ray (1960)	Cobalt 60
Weeks 50%	27.6	28.6
95% Fiducial Limits (weeks)	26.8–28.4	27.8–29.4
Chi Square Degrees of Freedom	3.6 (6)	1.5 (4)
Probability	>0.7	>0.8

Table II

RESULTS OF PROBIT ANALYSIS, SEPARATE CATARACT STAGES, DIVIDED TREATMENT, 1,500 RADS

Per Cent of 1+ or Greater Cataract

	X ray	Cobalt 60
Weeks for 50%	17.1	20.2
95% Fiducial Limits (weeks)	16.4–17.8	19.3–21.1
Chi Square Degrees of Freedom	17.2 (10)	0.8 (8)
Probability	>0.05	>0.99

Per Cent of 2+ or Greater Cataract

	X Ray	Cobalt 60
Weeks for 50%	27.3	
95% Fiducial Limits (weeks)	26.3–28.3	
Chi Square Degrees of Freedom	11.2 (12)	
Probability	>0.5	

Per Cent of 3+ or Greater Cataract

	X ray	Cobalt 60
Weeks for 50%	37.2	33.3
95% Fiducial Limits (weeks)	36.0–38.6	31.8–34.4
Chi Square Degrees of Freedom	9.1 (9)	16.4 (11)
Probability	>0.3	>0.1

Per Cent of 4+ or Greater Cataract

	X Ray	Cobalt 60
Weeks for 50%	43.8	45.4
95% Fiducial Limits (weeks)	42.2–45.8	44.1–46.9
Chi Square Degrees of Freedom	17.2 (13)	4.8 (8)
Probability	>0.1	>0.7

of radiation could be demonstrated.

If the classifications of 1+, 2+ etc. are considered as real numbers, an "average" can be obtained for the group as a whole. The "average" for the group at each time of observation can then be plotted as a function of the time after treatment. The pitfalls of such an arbitrary assignment of numbered values to biologic data have been discussed.[4] However, for the purpose of comparison of data and estimation of relative effects this approach was also tried.

The data of the two single doses of x radiation of 1959 and 1960 were considered a replicate experiment, because of results stated above, and therefore were pooled to give 1 x ray curve. This is shown in Figure 3, with the cobalt 60 results for comparison. The curves themselves were determined by probit analysis, using the "average" of 4+ as 100 per cent. The vertical lines on the points for the cobalt 60 curve are the standard errors, which give an estimate of the variability within the group of the degree of cataract production at any one observation date.

The numerical results of the analyses are given in the first part of Table III. The weeks for an "average" cataract of 2+, which corresponds to the 50 per cent value in a probit analysis, are very close. The fiducial limits overlap throughout almost the whole band, and there is thus no difference demonstrated between the two qualities of radiation by this method.

The second part of Table III gives the results for the divided treatments. Again there is wide overlapping of the 95 per cent fiducial limits, indicating no significant difference between 1,500 rads of x radiation or of cobalt 60 gamma radiation on this divided schedule.

Nonsignificant differences were thus found between the cobalt 60 gamma ray and the x ray results within the 95 per cent fiducial limits for most of the separate stage data, and for all the "average" curves. It is, therefore, reasonable to estimate the relative biologic effectiveness as unity.

Variables such as dose distribution, dose rate, biologic effect, and irradiated tissue

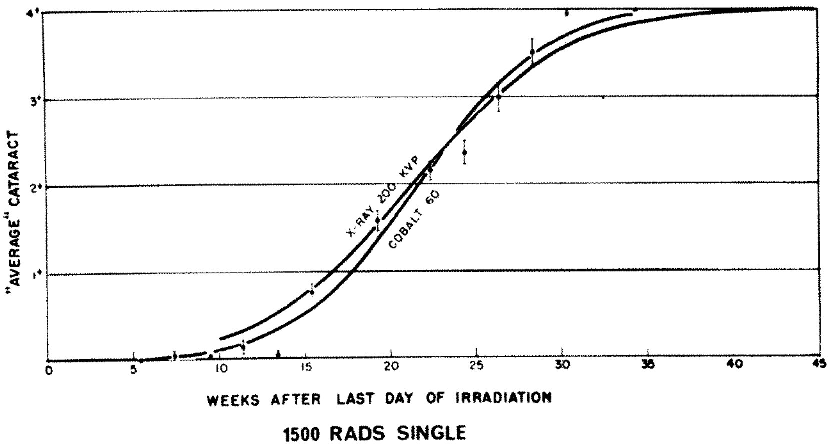

FIG. 3. A comparison of the pooled x ray results and the cobalt 60 experiments with single treatments. The points are for the gamma radiation of cobalt 60. The points for the x ray curve are not drawn since they would overcrowd the figure.

were the same or very close for the two qualities of radiation. Thus any difference in the RBE would probably have been due to differences in the linear energy transfer (LET). The mean LET of the primary x ray beam was approximately 1.8 kev. per micron in water, and that of the primary cobalt 60 radiation about 0.27 kev. The part of the RBE which depends on the LET is called the quality factor (QF). In the present experiment therefore, the QF also was estimated to be unity. Systematic errors in dosimetry and the conversion factor for absorbed dose are estimated to affect the accuracy of the stated dose by about ± 4 per cent. A method of analysis of error for the RBE is given in the Appendix.

SUMMARY

The relative biologic effectiveness of cobalt 60 gamma radiation of 200 kvp. x radiation at a half value layer of 1.0 mm. copper was determined for the induction of cataracts in rats. Groups of 25 to 30 animals were used for each quality and quantity of radiation. Single and divided doses of 1,500 rads of cobalt 60 radiation were compared with the same dose and treatment time for x radiation. The animals were examined before exposure and every few weeks thereafter.

Statistical analysis of the results showed no significant difference between the two energies of radiation. Therefore, in this study the RBE was unity for cobalt 60 gamma radiation compared to 200 kvp. x radiation for the induction of cataracts in the rat lens at a dose of 1,500 rads with single or divided treatments as described.

TABLE III

RESULTS OF PROBIT ANALYSIS: "AVERAGE" CATARACTS

	X ray	Cobalt 60
Single Treatment, 1,500 rads		
Weeks for 2+ Cataract	21.4	21.7
95% Fiducial Limits (weeks)	20.6–22.2	20.5–22.9
Chi Square Degrees of Freedom	24.9 (30)	2.7 (11)
Probability	>0.7	>0.99
Divided Treatment, 1,500 rads		
Weeks for 2+ Cataract	29.9	30.8
95% Fiducial Limits (weeks)	28.2–31.6	29.2–32.4
Chi Square Degrees of Freedom	19.2 (23)	10.8 (15)
Probability	>0.5	>0.7

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APPENDIX

The error of the RBE estimate has been obtained by utilizing the data on the several doses of 250 kv. x rays; 500, 1,000, 1,500, and 2,000 rads, given in single and divided forms; and the one dose for cobalt 60, 1,500 rads, given in single and divided form. Cataract development was measured from the data by a probit analysis of increase in incidence with time at a specific stage of cataractogenesis. There were usually four points for the analysis at each level of dosage, and only those probit lines were accepted which met the appropriate Chi-Square criterion for goodness of fit (Table I).

For the error of the RBE, isoeffect curves as described above and in the former publication[4] were obtained by plotting the log of the dose in rads against the log of the time at which 50 per cent of each group had reached the given cataract stage ($T_{50\%}$). The probit technique provides values for the latter parameter ($T_{50\%}$), as well as the variances for these parameters. The isoeffect curves are essentially linear over the range of dosage considered.

These isoeffect lines were computed by a least squares technique with each point of the line weighted by the reciprocal of the variance of the $T_{50\%}$ parameters; log dose was then taken as the independent variable. Thus the final equation for the isoeffect line was precisely balanced for the reliability of each point involved.

From the least squares isoeffect line, the variance of log time for the line was computed at 1,500 rads. The square root of this variance, equivalent to the standard deviation of log t_{50} at 1,500 rads, was added to and subtracted from the log $T_{50\%}$. The log doses corresponding to these upper and lower values were then calculated using the equation for the isoeffect line. After transforming from log dose to dose, the difference in dose was taken as the "uncertainty" in the dosage, that is, the range of dosage which gave, within the limits of experimental error, the same $T_{50\%}$. Here, experimental means biologic error plus variability of the observer's grading of a cataract.

The computations described above for the error of the RBE associated with x radiation were repeated for cobalt 60. Since cobalt 60 was used at 1,500 rads only, it was necessary to assume that the isoeffect line for cobalt 60 would have been parallel to the x ray isoeffect line in the region of 1,500 rads. As mentioned above, other investigators[17] have shown x ray dose changes in this range to have about the same sensitivity as cobalt 60. In the present experiment, dividing the dose made the same difference for cobalt 60 as for x ray.

Thus an isoeffect line for cobalt 60 was postulated by passing it through the cobalt 60 point at log 1,500 rads, log $T_{50\%}$, with a slope equal to that of the isoeffect line for x rays. The variance associated with the constructed isoeffect line was taken as the variance for the $T_{50\%}$ parameter derived from the probit analysis for cobalt 60. The upper and lower limits for log $T_{50\%}$ were then found and the corresponding range of dosage calculated similarly to that for the x radiation parameters.

Finally, with the estimated "experimental errors" in dose for both x rays and cobalt 60, the error in the RBE was obtained from the equation:

$$\text{Error} = \frac{A}{B}\left[\frac{a^2}{A^2} + \frac{b^2}{B^2}\right]^{\frac{1}{2}}.$$

where a and b are the "errors" for x ray and for cobalt 60 as calculated above, and A and B are both equal to 1,500 rads.

Since the doses also contain a dosimetry error of 4 per cent apart from the experimental variance which has been described above, this error was squared and added to the experimental variance to provide a more conservative figure for total variance due to dose.

The analysis as outlined was performed at those stages of cataract development at which there was a good cobalt 60 point and at least 3 good x ray points at different dosages. This was possible for the 3+ stage with the divided doses, for which the error for the RBE of unity was 6 per cent; the 1+ stage with divided doses, for which it was 16 per cent; and the 2+ stage with the single irradiations for which it was 9 per cent. The data for the 2+ and 3+ stages are considered more valid since the accuracy of observation of the earliest development of cataract at the 1+ stage is less definite.

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POSITIVE SCINTIGRAPHY OF TUMOR BY MEANS OF INTRA-ARTERIAL INJECTION OF RADIO-IODINATED MACROAGGREGATED ALBUMIN (MAA)*

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POSITIVE scintigraphy is not always successful in delineating neoplasms. At present it is used clinically in brain lesions, in certain thyroid carcinoma metastases and in certain lung tumors.[2] Sometimes radioiodinated human serum albumin produces a positive scintiscan,[3] but this is unusual.

I^{131}-MAA (macroaggregated albumin) was first devised by Benacerraf *et al.*[1] and later applied by Taplin *et al.*[5] to demonstrate the distribution of pulmonary circulation by intravenous injection. We reported our method in a previous paper concerning cases of pulmonary cancer,[4] where scanning was repeated daily after introduction of radioiodinated MAA into the arteries of areas in which the possibility of neoplastic disease was suspected. During the daily scanning, the intensity of radioactivity diminished more rapidly from non-neoplastic tissue than from the neoplasm. Finally the area of neoplastic tissue became much more prominently demonstrated, because it retained the radioiodinated MAA much longer. The importance of repeated scanning is thus clearly shown for the differentiation between neoplastic and non-neoplastic disease. This finding suggested to us that its use in other neoplasms should be investigated.

MATERIAL AND METHOD

Fifty-five subjects with various diseases were studied. Forty-four had neoplasms and 11 were non-neoplastic. The diagnosis in all was proven by operation or histologically, except 2 cases of pancreatitis and a normal subject. The material is summarized in Table I.

Percutaneous selective arteriography was performed by means of Seldinger's technique using Ödman's catheter (KIFA), red, green or yellow, according to the various arteries catheterized. I^{131}-MAA, 25 μ in size and 100 μc per mg. (made by Daiichi Pure Chemicals Co., Ltd., Japan), was injected into the arteries through the catheter. Attempts were made to inject branches of artery that included the vascular bed of the tumor or region of interest.

The carotid artery was directly punctured upstream from a brain tumor or maxillary cancer and I^{131}-MAA was injected through the needle. Bronchial arteries were catheterized with the red catheter for lung tumors. The other arteries were catheterized as follows: the celiac artery for liver, pancreas and stomach cancers; the superior mesenteric artery for pancreas and colonic tumors or mesenteric lymph node metastasis; the renal artery for renal tumors; the inferior mesenteric artery for rectal cancer and the internal iliac arteries for cancer of the uterine cervix. Yellow or green catheters were used and I^{131}-MAA was injected through the catheter. In most cases the dose was 250 μc for carotid and bronchial arteries, and 500 μc for other arteries. One to 5 mc of I^{131}-MAA of high specific activity (1,000 μc per mg.) was injected in some cases. I^{125}-MAA was also employed in the selected cases in order to make autoradiographic examination possible after removal of the specimen.

Immediately after the injection the

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Table I

POSITIVE SCINTIGRAPHY IN VARIOUS DISEASES

Disease	Arteries Injected with Radioiodinated MAA	Scintigraphy				Total
		+++	++	+	−	
Neoplastic Disease						
Brain Tumor	Carotid Artery		2			2
Maxillary Cancer	Carotid Artery	1				1
Primary Lung Cancer	Bronchial and Intercostal Arteries	3	1	1		5
Metastatic Lung Cancer	Bronchial and Intercostal Arteries		1			1
Stomach Cancer	Celiac Artery	2	2	2	1	7
Reticulosarcoma	Celiac Artery	1	1			2
Primary Liver Cancer	Celiac Artery	3	1			4
Metastatic Liver Cancer	Celiac Artery	2	5	1		8
Pancreas Tumor	Celiac Artery	2		2		4
Mesenteric Lymph Node Metastasis of Stomach Cancer	Superior Mesenteric Artery		1			1
Cecal Tumor	Superior Mesenteric Artery		1			1
Renal Tumor	Renal Artery		2			2
Rectal Cancer	Inferior Mesenteric Artery			1		1
Uterine Cancer	Internal Iliac Arteries		3	1	1	5
Subtotal		14	20	8	2	44
Percentage (%)		31.8	45.5	18.2	4.5	100.0
Non-Neoplastic Disease						
Lung Abscess	Bronchial and Intercostal Arteries				1	1
Duodenal Ulcer	Celiac Artery				1	1
Splenomegaly	Celiac Artery				2	2
Cholecystopathy	Celiac Artery				1	1
Gall Stone	Celiac Artery and Superior Mesenteric Artery			1	1	2
Pancreatitis	Celiac Artery				1	1
	Celiac Artery and Superior Mesenteric Artery			1		1
Cecal Adhesion	Superior Mesenteric Artery			1		1
Normal	Celiac Artery				1	1
Subtotal				3	8	11
Percentage (%)				27.3	72.7	100.0
Total		14	20	11	10	55

distribution of I^{131}-MAA was ascertained by linear and area scanning. Scanning was repeated daily until the tumor was positively delineated or for at least 2 weeks if this did not occur. After injection, nonradioactive iodine was given to saturate the thyroid gland. Urine was collected and measured for excreted free radioactive iodine. In the operated cases, the specimen was examined for the distribution of the radioactive materials, and the activity in normal and tumor tissues was compared.

RESULTS

In most of the cases of neoplasm, positive scintigraphy was obtained. The results are summarized in Table 1. They are evaluated by a four category grading system: *excellent* (+++), if scintigraphy definitely delineated a neoplasm; *fair positive* (++), if scintigraphy revealed definite tumor uptake in a neoplasm but with slightly ill-defined borders or with only partial delineation; *poor positive* (+), if scintigraphy showed the activity over a tumor to be at least higher than over normal tissue; and *negative* (−), if scintigraphy showed the activity over the tumor to be equal to the background activity.

Three cases of excellent positive scintigraphy (+++) are illustrated below.

REPORT OF CASES

Case 1. Female, 56 years of age, with diagnosis of bronchogenic carcinoma. Right bronchial arteriogram showed tumor vessels and

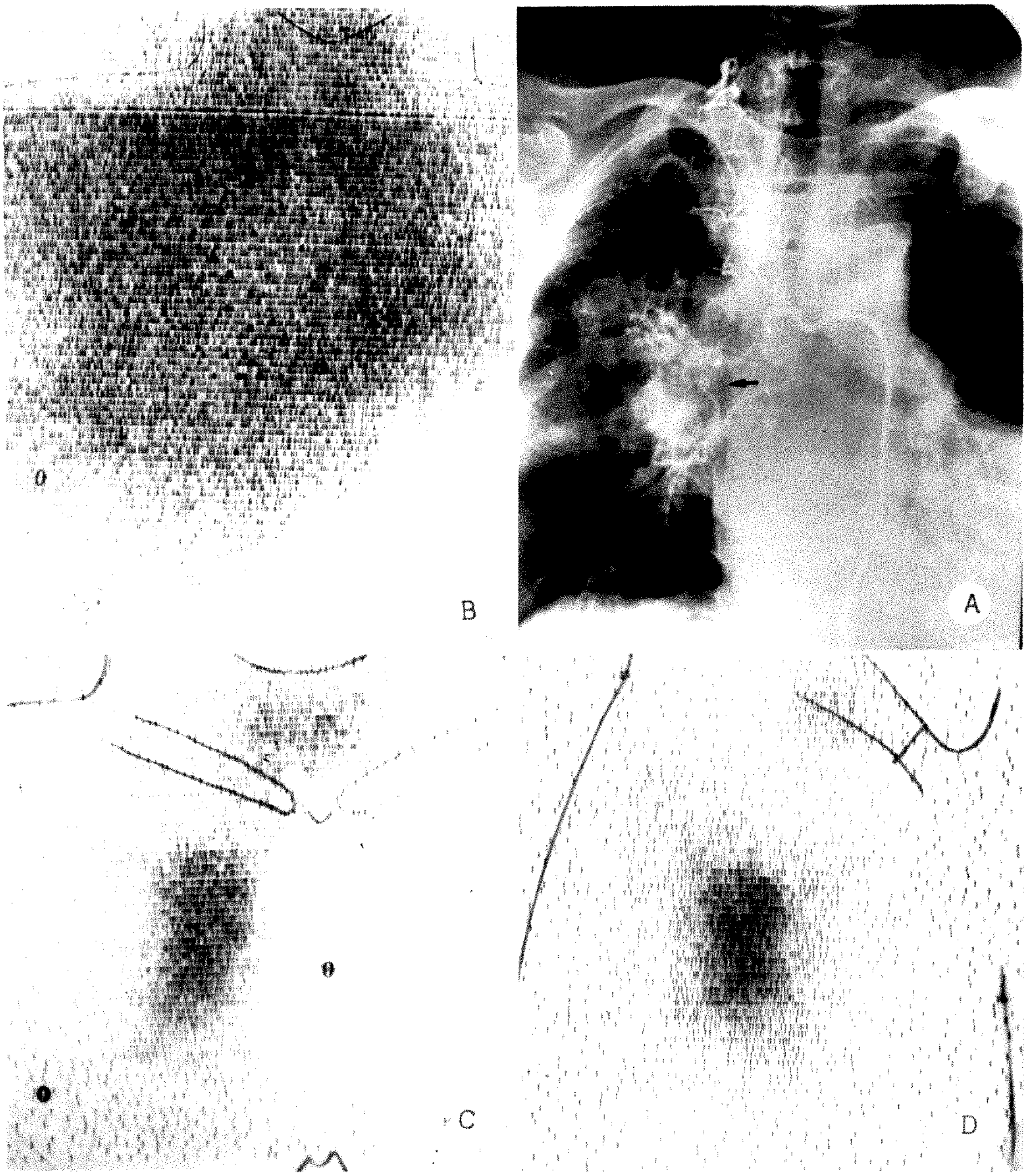

Fig. 1. Case 1. Bronchogenic carcinoma in a female, 56 years of age. (*A*) Right bronchial arteriogram. Tumor vessels and stains in the right hilar region (↑). (*B*) Scintigram in frontal projection, made after the injection of 250 μc I^{131}-MAA into the right bronchial artery. (*C*) Scintigram in frontal projection, made on 7th day after the injection. An area of tumor is clearly delineated. (*D*) Scintigram in lateral view.

stains in the right hilar region. A dose of 250 μc of I^{131}-MAA was injected into the artery, and its distribution was determined by scanning of the chest. The tumor was delineated on the 7th day after injection both in the frontal and lateral projections, and was superimposable on the corresponding shadow on the chest roentgenograms. This positive scintigram has not disappeared 14 days after the injection (Fig. 1, *A-D*).

Case ii. Male, 58 years of age, with diagnosis of gastric cancer. The tumor was situated on the lesser curvature in the upper body of the stomach. Celiac arteriogram showed slight increase of vascularity and tumor stains in the venous phase. I^{131}-MAA was injected into the artery in a dose of 5 mc, of higher specific activity. The tumor was positively scanned *in vivo* on the 3rd day after the injection. The higher radioactivity was even better shown in the tumor area of the resected specimen of the stomach (Fig. 2, *A-D*).

Case iii. Male, 63 years of age, with diagnosis of cancer of the head of the pancreas. Celiac arteriogram showed no significant increase of vascularity in the tumor. A dose of 500 μc of I^{125}-MAA was injected into the artery and the tumor was positively scanned on the 4th day after injection. The patient died on the 7th day due to severe jaundice, complicated by hemorrhage into the gallbladder and gastrointestinal tract. Scanning of the removed pancreas at autopsy and macro-autoradiogram demonstrated higher radioactivity localized in the tumor area (Fig. 3, *A-D*).

Comment. The differential absorption ratio of neoplastic and normal tissues (comparison of counts per gram of each tissue) measured by well-type scintillation counter, was: 4.5 times in hepatoma on 2nd day; 10.8 times in stomach cancer on 3rd day; 8.7 times in cecal tumor on 4th day; 6.4 times in cancer of pancreas on 7th day; and 22.4 times in insuloma (islet adenoma) on 4th day. On the other hand, in the case of duodenal ulcer the activity was 6.8 times less in the ulcer than in the normal duodenum on 4th day after injection. Most of the radioiodine was excreted in the urine within 2 days. The amount was greatest on the 2nd day.

DISCUSSION

The retention of radioiodinated MAA by many neoplasms appears to be of significance for two reasons: possibility of detection of the tumor and basic research into the peculiar vascularity of tumors which might lead to an improved therapeutic approach.

In our non-neoplastic series, 8 of 11 cases were negative (72.7 per cent) and the remaining were pseudo-positive (27.3 per cent). In the neoplastic series, however, only 2 of 44 cases were negative (4.5 per cent), and all the others were positive (95.5 per cent). Leaving aside the one plus (+) group, 34 of 44 neoplastic cases (77.3 per cent) were positive and thus the non-neoplastic cases could be differentiated from the neoplastic cases.

By micro-autoradiographic technique, we have found large colloidal particles of I^{131}-MAA in the capillaries adjacent to the tumor cells 3 days after injection, when the capillaries in the normal adjacent tissue were essentially clear. This finding suggests that the vascular drainage mechanism of colloidal particles in neoplasms is somewhat different from that in normal tissue.

SUMMARY

Selective arterial catheterization by Seldinger's technique was performed in 52 cases, apart from 3 cases of carotid artery puncture, followed by injection of radioiodinated (I^{131}- or I^{125}-) MAA in doses of 250–500 μc (1–5 mc of higher specific activity) into the arteries through the catheter or needle.

Serial scintigraphy was made daily until the tumor became positively delineated from the surrounding normal tissue or for at least 2 weeks if this did not occur.

In most of the cases of tumor, a positive scintigram was obtained. Non-neoplastic cases were essentially negative. Surgically

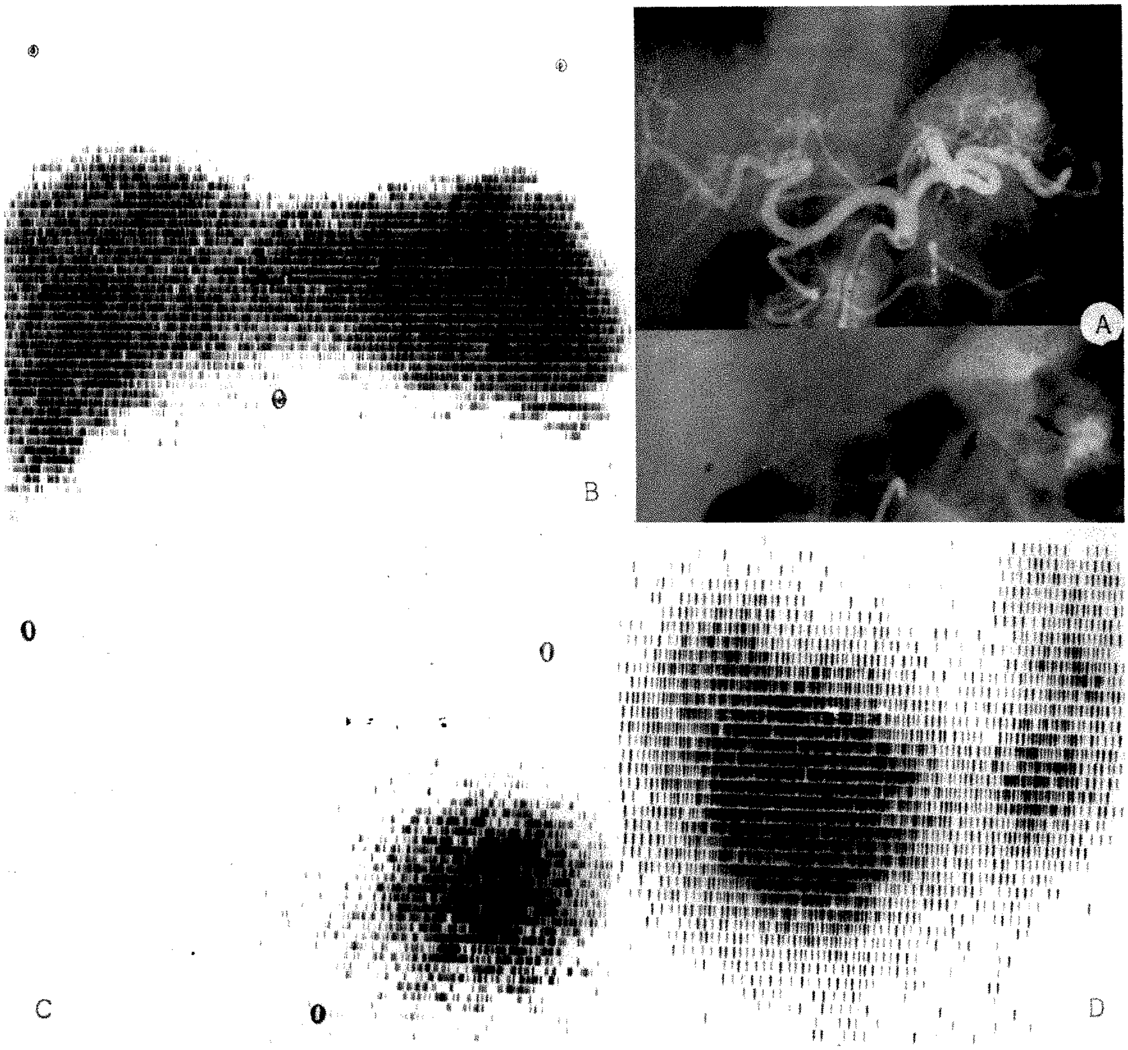

Fig. 2. Case II. Gastric carcinoma in a male, 58 years of age. (*A*) Celiac arteriograms. Slight vascular increase in arterial phase (↑), and tumor stains in venous phase (↑ ↑). (*B*) Scintigram made after the injection of 5 mc I^{131}-MAA into the celiac artery. (*C*) Scintigram made on 3rd day after the injection. Only the tumor is positively scanned. (*D*) Scintigram of the resected specimen of the stomach. The higher radioactivity is clearly shown in the tumor area.

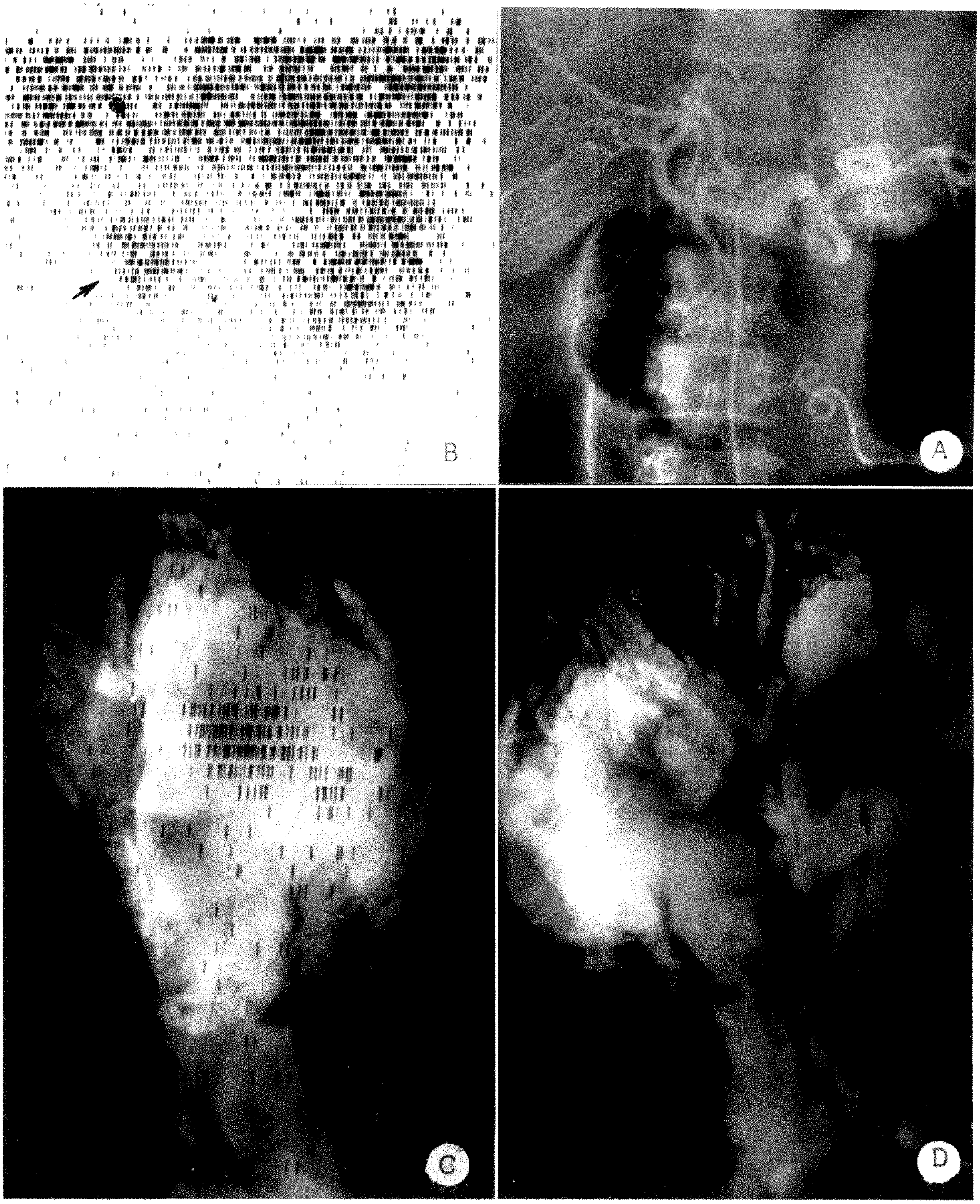

FIG. 3. Case III. Carcinoma of the head of the pancreas in a male, 63 years of age. (*A*) Celiac arteriogram. No significant vascular increase in the tumor. (*B*) Scintigram made on 4th day after the injection of 500 μc I^{125}-MAA into the celiac artery shows positive scan in the region of head of the pancreas (↑). (*C*) Scintigram of the removed pancreas superimposed on the roentgenogram (with soft rays) of the specimen. (*D*) Macro-autoradiogram of the sectioned pancreas shows higher radioactivity in the tumor area of the head of the pancreas (↑).

removed specimens contained higher radioactivity in the neoplastic tissues than in the normal or non-neoplastic tissues.

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RADIOALBUMIN MACROAGGREGATE BRAIN SCANNING*

A HISTOPATHOLOGIC INVESTIGATION

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IN 1964 Feindel *et al.*[3] concluded that "there are certain defects common to all methods involving radioisotopes for the localization of intracranial lesions. Tumors in the midline and posterior fossa are not in general well detected. This is due partly to the low level of uptake in the types of tumors commonly found in these regions." In their paper they reported on approximately equal results obtained using RISA, mercury 203, mercury 197 and radioneohydrin 197. Overton *et al.*[6] compared mercury 197 and mercury chlormerodrin 203 in clinical brain scanning but stated that the search would have to continue for better brain scanning agents which would produce less radiation to the patient generally and to the kidneys in particular. Day *et al.*[1] tried to prepare and label with iodine 131 a specific localizing antibody for human brain tumors but their end product was not sufficiently specific to be of practical use. Webber[9] described his experiences with technetium 99m but only discussed findings in normal subjects. Duggan *et al.*[2] used arsenic 74 and radioalbumin with somewhat poorer results than those obtained with other agents. Takahashi *et al.*[8] felt that they could differentiate meningiomas, astrocytomas, glioblastomas and metastasis to the cerebrum in their scans with mercury chlormerodrin 203 and mercury chlormerodrin 197.

Neurosurgeons and neurologists, however, have come to the conclusion that with this type of study, in which a greater concentration of the radioisotope in the tumor or in adjacent necrotic tissue is desired, no real advantage is found over ventriculography and arteriography nor can these studies be dispensed with. In addition, in the case of mercurial agents, it is pointed out that at best they are potentially harmful to the kidneys and are contraindicated in patients with a clinical history of renal disease. As a result, recent investigations in the field of brain scanning have been directed toward methods which delineate the distribution of the conserved vascular blood system and point up the presence of a hemorrhage, infarct or tumor by the negative area in the image obtained. Radioalbumin iodine 131 macroaggregates were first used for this purpose by Kennady and Taplin[4] in dogs, with macroaggregate particles which varied in size from 10 to 100 micra. They noted the possibility of untoward results from damage to cerebral tissue but concluded that the circulatory system of the dog was quite different from that of the human being. At the same time, when they sacrificed the 6 animals at 2, 3 and 5 months after the intra-arterial injection they could find no gross or microscopic alterations in the brain. Later, the same authors[5] reported on similar studies carried out in monkeys, again without subsequent clinical or histopathologic data of brain damage. They emphasized the need of more animal experimentation before employing this method in human patients. This warning came after Rosenthall[7] had already reported on his experiences with the same method in 15 patients who were all criti-

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cally ill with various types of disastrous intracranial pathology. Although Rosenthall concluded that this method revealed a hypoactive area in the scan which corresponded to the site of the pathology and that his results were better than those obtained by "conventional" scanning, he could not know, of course, whether the method by itself was producing any pathologic changes in cerebral tissue.

MATERIALS AND METHODS

We set out to investigate this factor with a rigid histopathologic control using rabbits as the experimental animals. Our series included 30 animals with body weight between 1,200 and 2,000 grams. They were guaranteed to be healthy on receipt from the animal farm and were observed for several days before entering the experiment to be sure that there were no clinical signs of disease. Nonetheless, we eventually had to eliminate 2 animals from the series because the autopsy revealed pre-existent, bilateral, nonspecific encephalitis, and 3 others because they died during the operative procedure. The effective number of animals was thus reduced to 25.

When Rosenthall carried out the method with human patients he used 30–100 μc of human radioalbumin macroaggregates injected into the right carotid artery. We decided to employ 5 to 10 times this absolute dose in order to exaggerate the danger of macro- or microinfarcts, if indeed this possibility existed.

ANATOMY

In the course of our transoperative and postmortem dissections in rabbits we found that the right and left common carotid arteries arise from the aortic arch, follow an ascending course immediately adjacent to the trachea on either side, disappear behind and above the mandibular angle and enter a rudimentary circle of Willis at the base of the brain. Only 1 rabbit in this series had division of the common carotid artery into an internal and external branch. The circle of Willis was made up of very small anastomosing arteries with hardly the gauge of a no. 27 needle. Nevertheless, in 2 animals (No. 23 and 24) it proved to be an effective anastomosis between the middle cerebral arteries since the autoradiographic studies revealed an equal number of macroaggregate emboli in both cerebral hemispheres.

OPERATIVE PROCEDURE

After intravenous nembutal anesthesia (50 to 125 mg.) we made a 3 cm. incision over the right sternomastoid muscle following its anterior border. The right carotid artery was isolated using blunt dissection and avoiding blood vessel ligation. The artery was underlaid with a fine polyethylene tube. Purse string sutures were placed in adjacent facia and muscle layers to prepare them for closure over the puncture area.

The radioalbumin macroaggregates were prepared in our laboratory and were made up of particles measuring 25 to 50 micra in greatest diameter; each batch prepared was subject to microscopic control. The dose to be used was placed in a 1 to 2 cc. volume in a 5 cc. syringe and the injection of the carotid artery was effected using a no. 26 needle. The moment the needle entered the vessel, lumen blood surged back into the syringe and a slow injection (1 to 2 minutes) of the macroaggregates was effected.

The animals were sacrificed at intervals which ranged from 5 minutes to 10 days after the injection. If survival for more than 2 hours was planned, the surgical wound was closed in anatomic layers with almost no blood loss. In animals killed at periods of 5 minutes to 2 hours, radioautographs gave equally good results. After 2 hours the macroaggregate activity diminished so rapidly that this procedure, for practical purposes, was negative.

The time intervals used were determined so as to establish the distribution of the macroaggregate emboli by autoradiographic means (in animals sacrificed at 2 hours or less), to detect macro- and microscopic

data of necrosis, hemorrhage or inflammatory reaction in the brain tissue (which does not appear until about 10 or 12 hours after the onset of focal anoxia), and to detect clinical data of cerebral insufficiency. It was decided that for this latter purpose a 10 day normal survival was more than sufficient and from the pathologic point of view there seemed to be no purpose in delaying the animal sacrifice for a period of months.

The animals were killed with intravenous nembutal, the brain was removed intact within 5 minutes, sectioned into right and left halves and fixed in 10 per cent formalin in separate jars for 12 to 24 hours. The tissue slices, labeled "right" and "left," were then processed as follows:

1. Routine dehydration and embedding in paraffin blocks.
2. The paraffin blocks are cut at 6 micra on the microtome and the slices mounted on standard slides.
3. Routine hematoxylin and eosin staining.

Radioautographs

4. After the last absolute alcohol bath, instead of passing to xylene, the slides are dipped in a 0.3 per cent solution of celloidin in a 1 to 1 solution of ether-alcohol.
5. The slides are dried in air for 24 hours.
6. In the darkroom (use of a Wratten light permitted) the slides are covered with Kodak NTB3 emulsion and immediately stored in a sealed black box in a refrigerator at −5°C. for periods of 48 to 96 hours.
7. The emulsion is developed in the darkroom with Kodak D-19 developer and fixed with Kodak Fixer (general purpose, hardening). The developing time is 6 minutes. The developer and fixer must be used at −4 to −5°C.
8. The slides are then washed in cold water for 1 hour.
9. Dehydration through alcohol at 96°C., absolute alcohol and xylene.
10. Coverslips are fixed over the emulsion layer with resin.
11. The slides are examined microscopically.

RESULTS

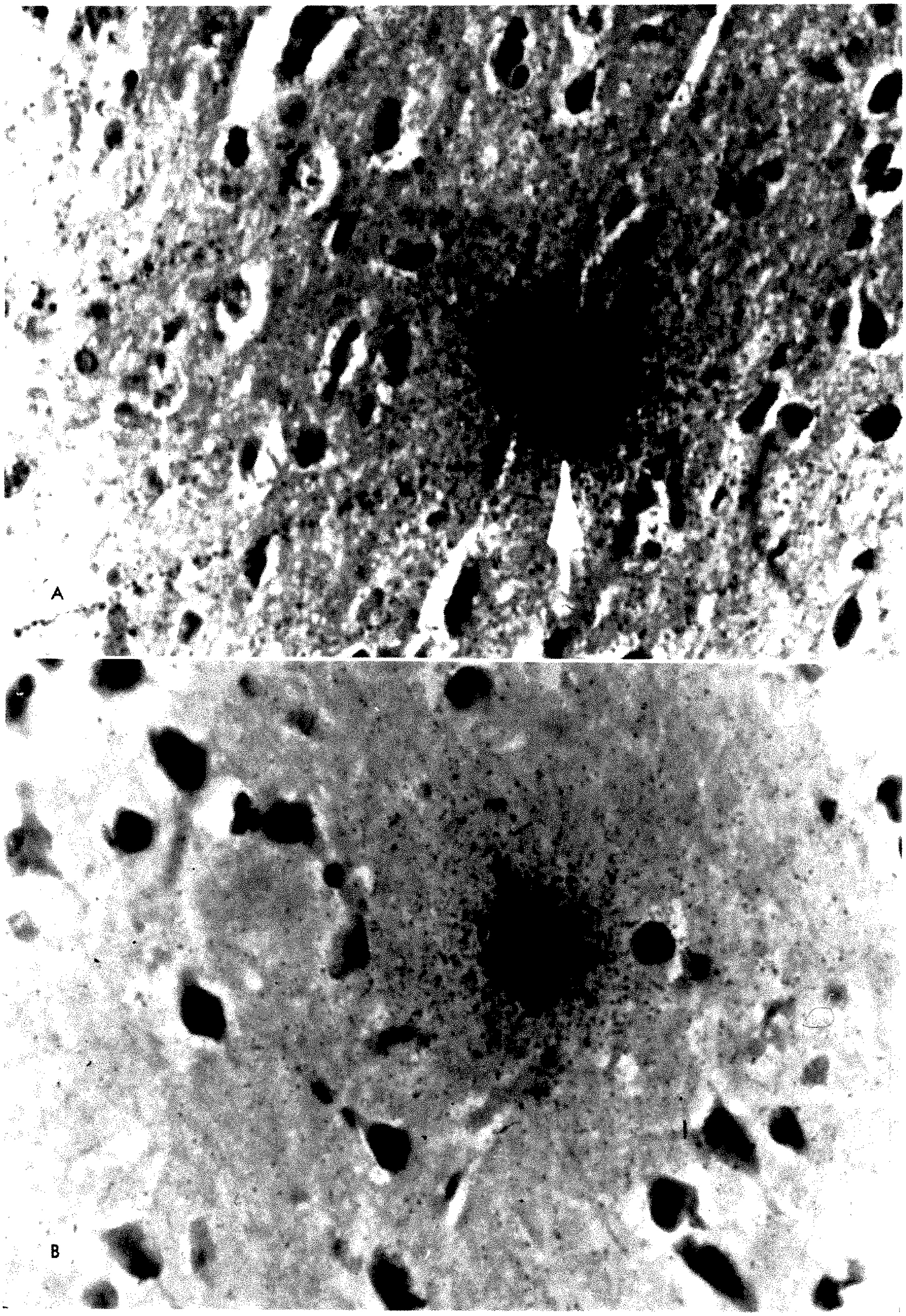
In the animals allowed to regain consciousness and live for periods ranging from 6 hours to 10 days, no clinical signs of brain damage were noted. The 18 animals in this category were completely awake at 6 hours and moving about; they were eating and drinking in normal fashion at 12 hours after surgery. Pupil size and reflexes were normal and equal in all animals before and after surgery.

There were no gross pathologic findings.

In the animals killed at 2 hours or less, the microscopic examination by the autoradiographs revealed the presence of macroaggregate microemboli in capillaries in both white and gray matter (Fig. 1, *A* and *B*) in all the cerebral lobes but not in the cerebellum. In 2 of the 7 animals in which autoradiographs were positive, the macroaggregate distribution was bilateral and equal. In the other 5, it was limited to the side of injection. The distribution of the macroaggregates was not uniform in 1 plane, about 1 capillary in 50 being occupied. Nonetheless, the distribution was apparently uniform for practical purposes in normal brain tissue as seen in a 3 plane projection.

In all animals, examination was made of multiple slides representing both cerebral and cerebellar hemispheres. At no time did we find any microscopic evidence of anoxia or infarct. There was no hemorrhage, necrosis or inflammatory reaction. In 3 animals, we performed Weil's stain for myelin in tissue blocks from each cerebral

FIG. 1. (*A* and *B*) The microphotographs are from rabbit cerebral cortex and show the radioautographic image of microemboli of radioalbumin macroaggregates in an animal sacrificed 2 hours after direct injection of 500 microcuries in the right carotid artery. The macroaggreates occupy capillaries and spill out into the adjacent ground substance. There are no histopathologic signs of edema, necrosis or hemorrhage (×450).


A
B

hemisphere and established that there was very little myelin in the rabbit brain but found the same quantitative and qualitative normal results in all tissues examined.

CONCLUSIONS

1. Radioalbumin iodine 131 macroaggregates were injected into the right carotid artery in 25 rabbits and immediately lodged in capillaries in both the gray and white matter in one or both cerebral hemispheres.

2. The macroaggregates were prepared in our laboratories and their greatest diameter ranged from 25 to 50 micra.

3. This procedure produced no clinical, gross pathologic or microscopic alterations in the experimental animals.

4. We believe that this method, if performed using macroaggregates of the same size as we have employed, will not produce brain tissue damage and may well be utilized in human patients.

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SEQUENTIAL BRAIN SCANNING IN RADIATION THERAPY OF MALIGNANT TUMORS OF THE BRAIN*

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THE worthiness of brain scanning as a screening procedure for neoplastic and other space-occupying lesions within the cranium has been well established. The selective increased uptake at the level of the lesion[5] presumably depends upon the local hypervascularity or increased vascular permeability.[1,6] Correlated with the clinical picture and additional diagnostic media (carotid and vertebral arteriography, pneumoencephalography, etc.) brain scanning has exhibited a high degree of diagnostic efficiency short of craniotomy.

It appears timely that, with the advent of simplified and perfected techniques of brain scanning and the absence of serious deleterious effects, the repetition of this study at short intervals be performed. This procedure becomes useful not only in detection of the lesion but also as an index of the therapeutic response. The potential usefulness of brain scanning in the planning of radiation therapy for intracerebral tumors, with the succeeding follow-up, appears to be gaining acceptance.[6]

CLINICAL MATERIAL AND METHODS

To further establish the place of systematic utilization of sequential brain scanning, 35 records of patients who had primary or metastatic tumor to the brain were analyzed. Table I reveals the distribution of this clinical material. Thirteen patients were treated for primary tumors of the cranium, and an additional 22 had metastatic lesions with a predominance of cancer of the lung and breast. All patients undergoing craniotomy had repeated brain scanning preceding the course of irradiation. It was thought of interest to compare the degree of abnormal uptake at the site of the known tumor location after surgery and to identify the abnormalities resulting from surgical manipulation itself (deformity, scarring, etc.).

The scanning was repeated at the conclusion of radiation therapy, and performed again at intervals of 3 weeks, 6 weeks, 2 months, and 3 months thereafter. Simultaneously, the clinical condition of these patients was critically evaluated. It was noted that adequate information was present to analyze clinical response and observe changes in the sequential brain scans in 21 patients.

TREATMENT

In all patients with accessible tumors, craniotomy was performed to confirm the diagnosis or to achieve rapid decompression when signs of rapid increase of intracranial pressure were apparent. Without delay treatment followed and consisted of conventional kilovoltage roentgen therapy with a half-valve layer of 2.75 mm. Cu and a focal skin distance of 50 cm. When the whole brain was included in the beam, the dose consisted of 3,500 rads minimum, calculated at the midplane, and spread over 20 treatments (30 elapsed days). For more limited volumes, the dose was comparatively larger than that described.

In preference to conventional irradiation, the megavoltage treatment was administered with a cobalt 60 teletherapy unit at a source skin distance of 80 cm. In cases requiring irradiation of the entire neural axis, a combination of supervoltage irradiation to the cranium and conventional kilovoltage irradiation to the spine was

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TABLE I

DIAGNOSIS IN 35 PATIENTS CONSIDERED FOR IRRADIATION OF BRAIN TUMORS AFTER BRAIN SCANNING

Primary Brain Tumors		
Proven histology:		
Astrocytoma—Well differentiated	4	
Astrocytoma—Poorly differentiated	4	
Cerebellar sarcoma	1	
Ependymoma	1	
Meningioma of right temporal lobe	1	
No biopsy:		
"Suprasellar tumor"	1	
Pinealoma	1	
		13
Metastatic to Brain		
Carcinoma of the lung	9	
Carcinoma of the breast	8	
Malignant melanoma of skin	2	
Renal carcinoma	1	
Carcinoma of the colon	1	
Reticulum cell sarcoma	1	
		22
		35

utilized. However, the dose delivered with supervoltage irradiation fluctuated from 3,500 rads minimum midplane dose in 24 elapsed days to 5,500 rads minimum midplane dose in 45 elapsed days. The placement of the portals for treatment plus the volume was mainly governed by the lesion defined on the brain scans. The described irradiation has generally been well tolerated; more or less complete epilation, erythema, and dry desquamation were followed by regrowth of hair usually 3 months after the end of therapy.

CLINICAL OBSERVATION AND FOLLOW-UP BRAIN SCANS

An attempt to correlate the compiled data obtained through follow-up isotope encephalograms and the clinical response was made. Information procured through an analysis of these data is summarized in Table II. There appears to be an extremely high degree of correlation between the brain scans and the clinical condition of the patient following the course of radiation therapy. For example, in 18 patients an objective and subjective improvement of the clinical condition after treatment was observed. The brain scans in these patients indicated a decreased uptake in 3, and a reversion to "normal" in 15 instances, compared with the pretreatment scans. In the 3 patients no ostensible changes were apparent in their brain scans at the level of the irradiated lesions. Two of these patients subsequently developed recurrence which was detected during the follow-up brain scanning procedures. These lesions were described as either being larger, or as new lesions. It is of interest to note that these changes preceded a clinical manifestation of recurrence by periods of days to weeks. Conversely, when both the clinical condition and the appearance of the scan indicated an improvement, a late recurrence was detected in a single case 17 months after irradiation. These findings seem to suggest the usefulness of post treatment brain scanning even in estimating the prognosis. Three patients who did not respond clinically to radiation therapy had follow-up brain scans in which either an enlargement of the treated lesions or no objective changes were described. A single

TABLE II

CORRELATION OF CHANGES IN SEQUENTIAL SCANS AND THE CLINICAL RESPONSE TO RADIOTHERAPY IN 21 PATIENTS (FOLLOW-UP PERIOD FROM A FEW MONTHS TO 2 YEARS)

Clinically			
Improved		No Improvement	
Appearance of Scans		Appearance of Scans	
No Change	Decreased Uptake or Normal	No Change	Worse
3*	15†	2	1

* Subsequent recurrence in 2 patients.

† Clinical and isotope encephalographic recurrence in 1 patient 17 months after brain irradiation.

patient with biopsy-proven metastatic tumor to the posterior fossa had a normal brain scan prior to craniotomy, while the brain scan preceding irradiation was again reported negative for tumor, although changes derived from surgical manipulation were present. This patient has remained clinically well to the present time. In another patient with metastatic brain tumor, whose clinical condition deteriorated during the treatment, the brain scan obtained 3 weeks after initiation of therapy demonstrated a significant "worsening" of the appearance of the lesions, and therapy was discontinued.

Illustrative case. A 12 year old girl referred for brain scanning on April 5, 1965, exhibited an abnormal uptake in most of the temporal and the posterior parietal lobes (Fig. 1, *A* and *B*). The study was performed because she developed left hemiparesis, nausea, vomiting, diplopia, and papilledema. When biopsy confirmed a diagnosis of ependymoma, she received radiation therapy to the entire neural axis. Both cranium and spinal cord were irradiated to the cauda equina, combining cobalt 60 teletherapy and conventional kilovoltage roentgen therapy in the previously described fashion.

The young patient became well, showing complete clinical remission, and her successive brain scans (Fig. 1*C*) also remained apparently "normal" over a period of a year and a half after treatment.

However, further scanning of the brain on September 14, 1966, disclosed an area of definitely abnormal uptake (Fig. 1*D*). The abnormality now appeared to be in the frontal lobe, anterior and inferior to the previously treated

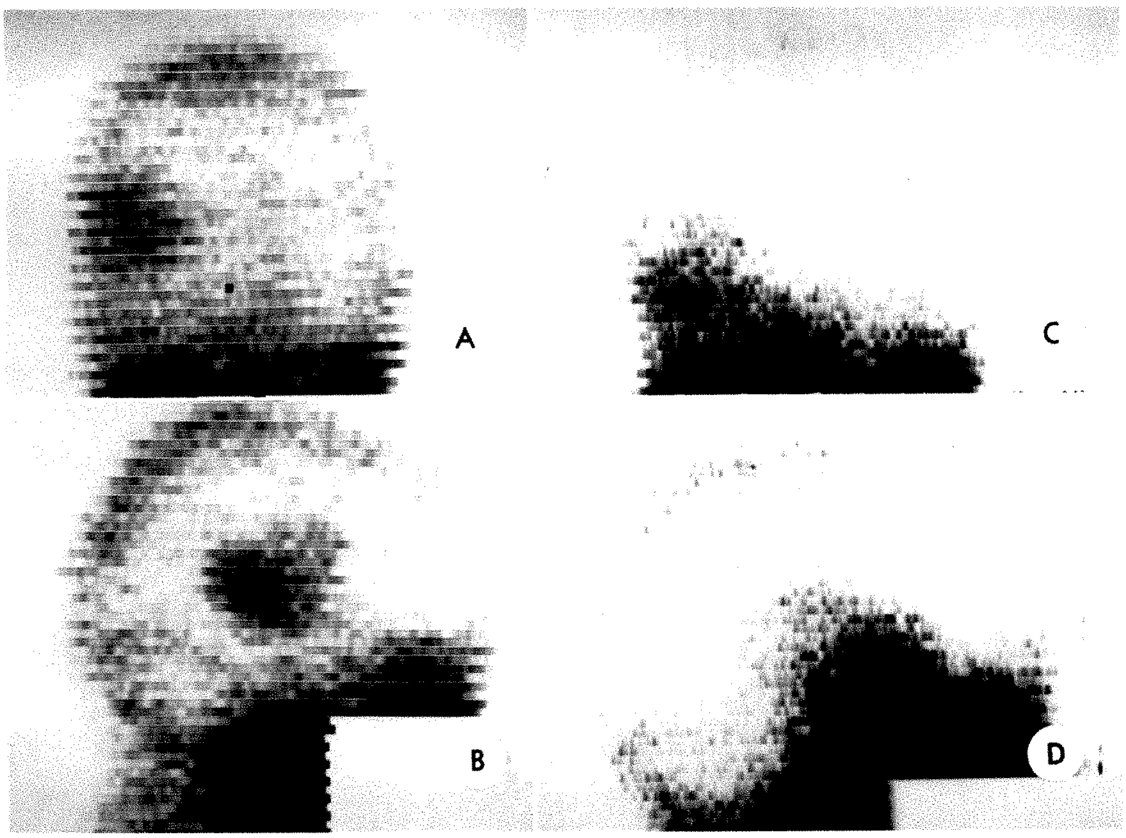

Fig. 1. (*A*) Frontal and (*B*) right lateral brain scans defining lesions due to increased uptake in the temporal and parietal lobes, preceding craniotomy for ependymoma. (*C*) One year later, following partial resection and radiation therapy. (*D*) A new area of increased uptake 18 months after treatment in the right postero-inferior portion of the frontal lobe indicates subsequently confirmed marginal recurrence.

lesion. Clinically, she complained of dizzy spells, nausea, and vomiting.

Because of the rapid worsening of her clinical condition and papilledema, she promptly was subjected to a second craniotomy on September 15, 1966. At this time a cystic-appearing tumor mass of 90 cc. was evacuated from the anterior and inferior frontal region.

Histologic examination of the specimen confirmed recurrent ependymoma, which exhibited some alteration of the histologic pattern attributed to irradiation.

She was recovering from her symptoms when last seen.

SUMMARY AND CONCLUSIONS

The isotope encephalogram obtained before surgery and radiation therapy from patients with primary or metastatic tumors of the brain furnishes valuable diagnostic criteria to the clinician. The pretreatment brain scan may contribute data of diagnostic value, but its authentic usefulness in treatment planning surpasses other diagnostic media by virtue of indicating the site and volume of the brain lesion to be irradiated.

A high index of reliability of the follow-up brain scans in 21 irradiated patients in predicting new sites of growth was evident. During the clinical remission, the areas of increased uptake reverted to "normal" or appeared markedly "improved" as compared with the pretreatment scans. The follow-up scans gave the impression of being unaltered for a time in 2 patients who did not respond to treatment, and were definitely worse in a single case with no clinical improvement during therapy.

The detection of recurrences after clinical remission invariably parallels the worsening of the image and pattern of the areas of uptake from a month to years post treatment. It is interesting to note that irradiation of the brain does not result in changes detectable on brain scans of the surrounding structures in the absence of tumor activity. The serial scanning using technetium 99m can be performed with equanimity, and the morbidity is nil. It is felt at this stage that the procedure is useful, and cumulative material conceivably will confirm that it is well indicated in radiation therapy of neoplastic processes of the brain.

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DEMONSTRATION OF THE CHOROID PLEXUS WITH TECHNETIUM 99M BRAIN SCAN*

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IN ITS infancy, brain scanning provided information of inconsistent reliability. Techniques were crude by present standards and the available radiopharmaceuticals, such as mercury chlormerodrin and I^{131} serum albumin yielded data statistically inadequate for good image quality.

Improved scanning technology together with newer agents, notably technetium 99m, has resulted in a remarkably improved capability to demonstrate intracranial abnormalities.[3] This advantage, however, is limited by the fact that, while the abnormal areas are revealed with greater clarity, certain normal structures previously unrecognized are now seen regularly, and may be a source of unwarranted concern to the unwary observer.

The pharmacology of Tc^{99m} pertechnetate has been the subject of intensive and continuing investigation. It has been established that the agent does not diffuse into normal brain substance. Sites of increased concentration reflect either a disruption of the blood-brain barrier, areas of abnormal vascularity or normal structures possessing great vascularity. One further mechanism, presently in the investigative stage, is that of active secretion of the isotope by discrete structures.[7]

Since the advent of technetium 99m the appearance of normal vascular structures such as the sagittal, lateral and cavernous sinuses has been amply documented.[4,6] Far less emphasis has been placed on the choroid plexus, which frequently is rerecorded with spectacular clarity. It is the purpose of the authors to focus attention on this neglected structure which may be a potential source of false positive interpretation.

MATERIAL AND METHOD

Technetium 99m is commercially marketed in several forms. In addition to the original "open" column of molybdenum 99, from which Tc^{99m} is eluted, a closed, pre-sterilized, pyrogen free system can be obtained. "Pre-milked", sterile calibrated Tc^{99m} is also available.

We are presently using a modified Picker 3×2 inch sodium iodide crystal rectilinear scanner equipped with an experimental low energy, high efficiency, high resolution 721 hole Brookhaven collimator.[1,5] The data blending technique is employed.[2] Scanning is begun 20 minutes following the intravenous administration of 10 mc of Tc^{99m}. We have not used potassium perchlorate as a blocking agent. The time required for each view is approximately 15 minutes.

ANATOMIC CONSIDERATIONS

The choroid plexus is composed of innumerable villous projections of the pia mater, covered by a layer of ependyma and richly permeated by a fine network of arterioles, capillaries and venules. The volume and geographic extent of the choroid is highly variable, and even in the same individual may differ greatly from side to side. For purposes of this discussion, the portion of the choroid contained within the lateral ventricles is of primary importance. Situated lateral to the midline, this segment of the choroid arises at the foramen of Monro, where it is contiguous with the choroid of the third ventricle. It then courses posteriorly along the floor of the lateral ventricle to the atrium, at which point it enlarges in bulbous fashion to form the glomus. The choroid then dips an-

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teriorly and inferiorly, and terminates in the roof of the temporal horn (Fig. 1, *A–C*).

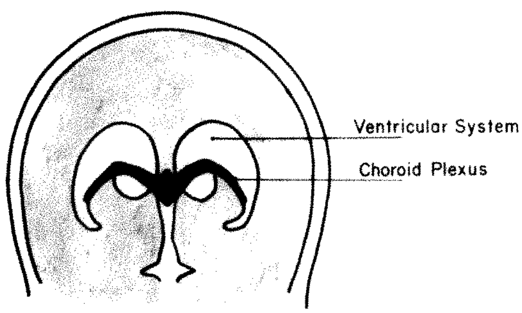
When viewed from the side, this choroid of the lateral ventricles has a "C" shaped configuration, a fact of considerable importance in its recognition on the brain scan. The choroid will rarely appear as an isolated structure. Large vascular pools, such as the great vein of Galen, are usually superimposed on the glomus in the lateral view (Fig. 2, *A–C*).

The main vascular supply of the choroid plexus arises directly from the internal carotid artery as the choroidal artery. The most posterior portion of the plexus derives its supply from choroidal branches of the posterior cerebral artery and the superior cerebellar vessels. The venous drainage of the choroid is towards the foramen of Monro (the venous angle) and then posteriorly to terminate eventually in the vein of Galen.

This rich vascular network, possibly abetted by active secretion of Tc^{99m} by the choroid, results in an enhancement of the counting rate throughout this area. Failure of the choroid to visualize on a repeat scan after the administration of perchlorate, which presumably blocks active choroidal Tc^{99m} secretion, aids in the differential evaluation. Similar information can be obtained by failure to demonstrate the density on a repeat scan with mercury chlormerodrin.[7] Nevertheless, the general configuration and location of the choroid as perceived by the scanner are so characteristic that once seen it is unlikely to be mistaken for anything else.

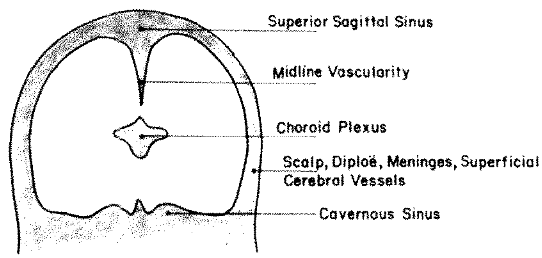
SUMMARY

With the advent of high resolution Tc^{99m} brain scans, the apparently normal concentration of activity within the choroid plexus is frequently visualized. The charac-



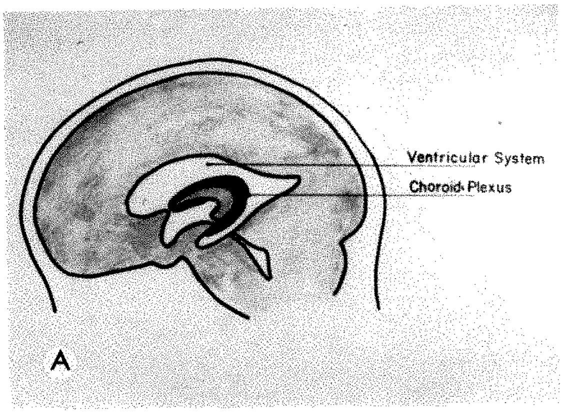
A

B



C

FIG. 1. (*A*) Normal anatomic relationships-anterior view. (*B*) Normal Tc^{99m} scan-anterior view. (*C*) Normal diagrammatic scan-anterior view.



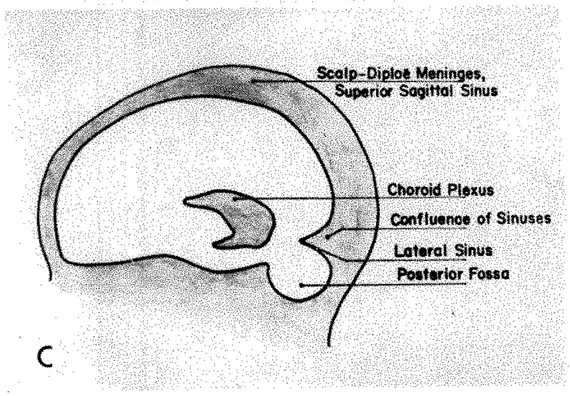


FIG. 2. (*A*) Normal anatomic relationships-lateral view. (*B*) Normal Tc^{99m} scan-lateral view. (*C*) Normal diagrammatic scan-lateral view.

teristic location and configuration are described. Care must be taken to differentiate this density from a pathologic process. An awareness of its normal appearance should prevent erroneous interpretation of this structure.

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THE ROLE OF RADIOTHERAPY IN THE MANAGEMENT OF MALIGNANT TUMORS OF THE SALIVARY GLANDS*

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THE role of radiotherapy in the management of malignant disease of the parotid gland has never been clearly defined. There are many references in the literature to the effect that cure or long term control of parotid gland malignancy is dependent on adequate surgery. Much less credit is given to adequate radiotherapy.

In a recent review evaluating histology *versus* prognosis by Patey *et al.*,[3] radiotherapy alone or as an ancillary treatment to surgery was given to some 66 per cent of the cases reported. This in itself suggests some doubt as to the adequacy of surgery alone. The authors throughout the text of this excellent paper make very fair comments on the contribution of radiotherapy. Patients enjoying long term control are divided fairly evenly between the groups treated by surgery plus radiotherapy, and surgery alone. Yet in their concluding summary the only mention of management is, I quote: "correct surgical treatment of the primary tumour should cure most cases of muco-epidermoid cylindromatous and acinic cell tumours." This apparent bias towards surgical management arises, one presumes, from two factors: (1) The bad impression due to the very poor prognosis of patients already beyond any form of surgery who terminally receive radiotherapy; and (2) the difficulty of assessment of the contribution of radiotherapy *versus* surgery in combined treatments.

It is in an attempt to evaluate the latter that a study has been made of all malignant tumors of the parotid gland which have been treated at the Christie Hospital during the years 1950–1961.

Adenocystic carcinoma (cylindroma) because of its rather different natural history[2] has been excluded from the main group and will be dealt with separately. Also excluded are all tumors of the reticuloendothelial system, as the merit of radiotherapy is not generally questioned in such cases (14 cases). Malignancies subsequent to or associated with mixed parotid tumors are few in number and have only been admitted on definite histologic evidence of malignancy. There were 11 cases where the pathology was not obtained. These have been excluded. Also excluded are 4 cases reported as sarcoma.

Currently a review of histology is taking place to bring our own classification in line with that of Foote and Frazell,[1] but as this is as yet incomplete a further histologic breakdown would be of little value at this time. This may not be the handicap that it might seem, for the lack of knowledge of the histology is the very problem that the surgeon has to face when making that most important first decision regarding surgical approach. It is generally accepted that to cut into any parotid tumor *in situ* is to court disaster, at least as far as subsequent surgery is concerned. Thus preoperative biopsy is not indicated and the initial decision must be made on an intelligent guess as to what the histology will prove to be. It is one thing to state "correct surgery should cure," it is quite another thing to define "correct." Few surgeons relish the idea of sacrificing the facial nerve, only later to find they have removed a benign tumor. This problem of initial decision is very real and at this time remains insoluble.

* Presented at the Forty-ninth Annual Meeting of the American Radium Society, Toronto, Ontario, Canada, May 29–31, 1967.
From Christie Hospital and Holt Radium Institute, Manchester, England.

I. CARCINOMA OF THE PAROTID GLAND

Seventy-nine cases of carcinoma of the parotid gland remain in this study and have been classified under two broad categories: Group 1, inoperable cases; and Group 2, operable cases.

Group 1 (in all, 49 cases) includes: 31 patients considered inoperable at the onset and who had only biopsy performed; and 18 patients who had previous surgery followed by recurrence, and who were considered beyond any further surgical approach.

High dose radiotherapy can only be given to relatively small volumes, and just as moderate extension prevents adequate surgery, so gross extension precludes adequate radiotherapy. This group has therefore been divided: (a) into those cases where tumor involvement was such that moderately high dose could be entertained (19 cases); and (b) those others to whom only the simplest palliative treatment could be given (30 cases). The results are given in Table I.

(a) Three cases in the more radically treated group are alive and well at 6+, 7+ and 10+ years respectively. In 9 cases the primary regressed and they remained well to death from metastases or intercurrent disease. In the remainder, recurrence developed but 4 of these in the more radical group had good palliation, their tumors being controlled for 4+, 4+, 6, and 7+ years respectively.

(b) Simple palliative treatments gave some relief of pain but, with 3 modest exceptions, there was no material benefit. The over-all picture in this group is depressing, but it must be realized that this is just as much a measure of the failure of surgery as it is of the failure of radiotherapy. In fact, any salvage here must be classed as a modest feather in the radiotherapist's cap.

As has been stated, the adequacy of radiotherapy is intimately connected with the extent of tumor involvement, and one suspects that had the 18 cases who had previous surgery been referred for immediate postoperative treatment, *i.e.*, when tumor involvement was minimal, the results might have been a little more promising.

Group 2 (in all, 30 cases) (Table II) includes:

(a) A small group of 5 cases, 1 of which had previous surgery plus radiotherapy, and 1 which had some preoperative radiotherapy. All had surgery. Four are well at 5, 10, 11 and 16 years. One died of intercurrent disease, primary well, at $1\frac{1}{2}$ years.

(b) A second group of 6 cases which, following surgery, being rated by the surgeons as potentially clear, had postoperative radiotherapy: 5 had radium needle implants, 1 had roentgen-ray therapy. Three are well at 10, 11 and 18 years. Three died, primary well, of intercurrent disease at 7/12, 9/12 and 7 years.

(c) The remaining 19 cases (Table III)

Table I

CARCINOMA OF PAROTID GLAND INOPERABLE

49 Cases

Biopsy only 31 cases; previous surgery failed 18 cases	
(a) Radical Radiotherapy Attempted	*3 Well 6+, 7+, 10+ years 6 Died P. W. 2× <1, 1+, 2+, 2+, 3+ years 10 Died P. Rec. 4× <2, 2+, 2+, 4+, 4+, 6, 7+ years
(b) Simple Palliative Radiotherapy Only	3 Died P. W. <1, 1+, 3+ 27 Died P. Rec. 25× <1, 2+, 3+

* No surgery, biopsy only. P.W.=Primary well. P.Rec.=Primary recurrence.

Table II

CARCINOMA OF PAROTID GLAND
OPERABLE AND POSTOPERATIVE POTENTIALLY WELL
11 Cases

(a) 5 Cases (1 previous surgery+radiotherapy; 1 preoperative radiotherapy)	
All treated by Surgery	4 Well at 5, 10, 11, 16 years 1 Died P. W., I. C. $1\frac{1}{2}$ years
(b) 6 Cases (2 previous surgery)	
All treated by Surgery+Radiotherapy	3 Well at 10, 11, 18 years 3 Died P. W., I. C. 7/12, $1\frac{3}{4}$, 7 years

P.W.=Primary well. I.C.=Intercurrent disease.

following operation were rated by the referring surgeons as potentially or definitely residual. Eight were treated by V-plane radium needle implantation (Fig. 1, *A* and *B*) to doses of 6,000–6,500 rads in 7 days. Eleven were treated by external radiotherapy over a dosage range of 4,000 rads given in 3 weeks with large fields to 5,800 rads tumor dose in 3 weeks to smaller volumes. Ten patients are alive and well at 6, 7, 8, 9, 4×10, 11 and 14 years. Four died, primary well, of intercurrent disease at 8, 9, 9 and 13+ years. Three died, primary well, of metastases at 11/12, $4\frac{1}{2}$ and $4\frac{3}{4}$ years. *Two only* died with primary disease recurring. One of these had lymph node involvement initially and the other had recurrence in depth, and in retrospect the target volume selected did not cover the site of recurrence.

Comment. On this evidence it would appear that radiotherapy may have a very definite role in the management of these tumors and that a combined treatment, surgery plus radiotherapy at the outset, may prove to be the optimum policy. The evidence, however, is not incontrovertible. The surgery only group is very small. This probably stems from the fact that the Christie Hospital is fundamentally a radiotherapy center. If in consequence our surgical colleagues here feel that further proof is necessary, a clinical trial of surgery *versus* surgery plus postoperative radiotherapy would be most welcome.

II. ADENOCYSTIC CARCINOMA (CYLINDROMA)

Turning now to adenocystic carcinoma (cylindroma) the task of evaluating the role of radiotherapy, or for that matter surgery, in the management of these

Table III

CARCINOMA OF PAROTID GLAND
OPERABLE AND POSTOPERATIVE RESIDUAL
19 Cases

(c) 19 Cases (1 case—3 operations; 2 cases—2 operations; the remainder 1)
All rated as residual postoperatively and treated with radiation
(8—V plane implants; 11—external radiotherapy)

10 Well	6, 7, 8, 9, 4×10, 11, 14, years
4 Died P. W., I. C.	8, 9, 9, 13+ years
3 Died P. W., Mets.	$\frac{11}{12}$, $4\frac{1}{2}$, $4\frac{3}{4}$
2 Died P. Rec.	$2\frac{1}{12}$, $3\frac{1}{2}$

P.W.=Primary well. I.C.=Intercurrent disease. Mets.=Metastasis. P.Rec.=Primary recurrence.

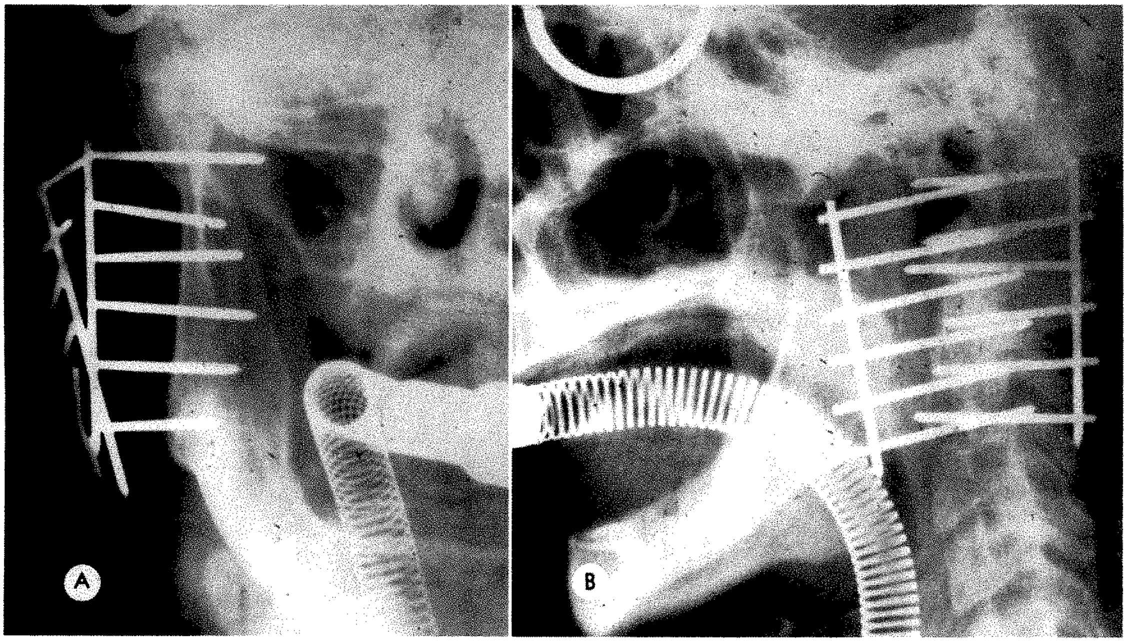


Fig. 1. V-plane radium needle implant to parotid gland. (*A*) Anteroposterior and (*B*) lateral roentgenograms.

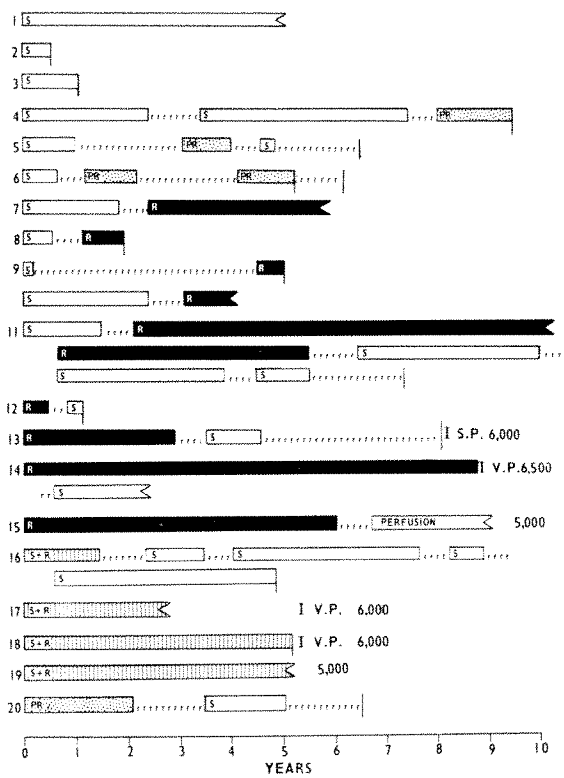
tumors is exceedingly difficult, for the following reasons:

1. The disease can extend over three decades or can lead to death within 1 year. This renders survival figures by themselves relatively meaningless.
2. Surgical accessibility and local radiation tolerance varies enormously from site to site, making it even more difficult to group cases for purposes of comparison.
3. The general policy over the years has been that where tumor is accessible, surgery should play the primary role, radiotherapy being reserved for inoperable or recurrent cases. This makes the comparison of like with like impossible.
4. The radiotherapeutic approach in respect of Target Volume, Technique and Dose has varied very considerably over the period in question, thus precluding grouping by treatment technique.

To give, therefore, any estimate of the relative value of radiotherapy *versus* surgery, it has been necessary to illustrate cases individually. This allows comparison between sequential treatments in the same individual and also some comparison between sites of origin. In the records of the hospital up to 1962 there are in all 94 cases where histologic diagnosis has been reasonably established. Some pre-1950 cases of suspected adenocystic carcinoma where histology has not been reviewed more recently have been excluded. Two cases where the histology of adenocystic carcinoma was confirmed only during the course of the disease have been admitted.

For the purposes of this study, interest has been restricted to the control of the primary growth and no attempt has been made to assess the management of secondary disease.

The duration of the symptom-free control of primary growth has been accepted as the criterion of success of treatment, and implies no progression of the primary growth during that period. Radiation doses, unless otherwise stated, are tumor doses in 3 weeks—implants in 7 days. In other cases the over-all time is stated in days in brackets.



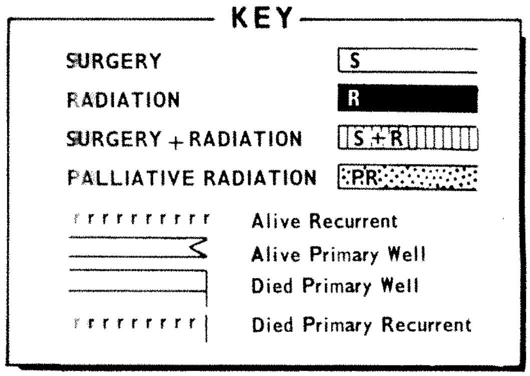


FIG. 2. Cylindroma of parotid gland. I S.P. = Single plane implant. I V.P. = V-plane implant.

PAROTID GLAND (Fig. 2)

The general picture is that of initial surgery followed by radiotherapy on recurrence. The honors with regard to control are shared roughly equally. It is interesting, however, that the duration of control exerted by initial surgery is frequently short and may compare unfavorably with surgery plus radiotherapy as the initial treatment. Case 11 illustrates an earlier point with regard to natural history. This tumor was excised, recurred in 2 years and then was subjected to radiotherapy at St. Bartholomew's Hospital, London in 1932 with a somewhat uncertain dose, which produced remission for 14 years. The tumor recurred in 1947, at which time the histology was established. Several attempts were made to eradicate the tumor by surgery, with some control. The patient ultimately died in 1960, 29 years from first treatment. The single plane radium needle implant in Case 13 compares unfavorably with the V-plane implants in Cases 17, 18, and 19—the target volume perhaps was too small. Case 15 in isolation is also of interest. After 6 years' control by radiation the primary recurred, was perfused with methotrexate, and when last seen the patient was still well at 9 years.

SUBMANDIBULAR GLAND (Fig. 3)

Again initial surgery is disappointing, and where it fails it usually does so within

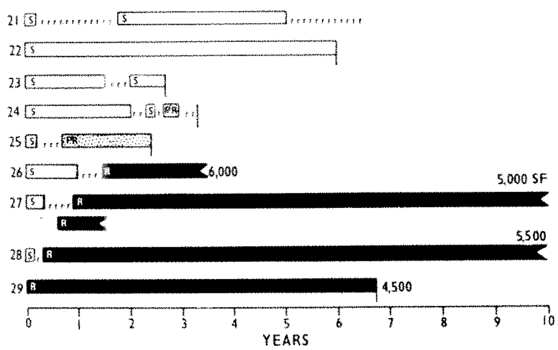


FIG. 3. Cylindroma of submandibular gland. SF = single field, given dose.

2 years. In Cases 26, 27, 28 and 29 control has been exerted by dosage ranging from 6,000 rads in 3 weeks to as low as 4,500 rads in a similar interval. Case 27 in particular was quoted as "being beyond any form of surgery" at the time when roentgen-ray therapy was given.

TONGUE AND FLOOR OF MOUTH (Fig. 4)

The surgical result is good in Cases 31, 32 and 33, and poor in Cases 30, 34 and 35. Case 30 had very radical surgery involving hemimandibulectomy but the lesion recurred very quickly. Radiotherapy had some success: 1 long term control and 2 cases controlled to death. Case 37 was treated by a tongue-pterygoid implant. This technique has now been superseded by external megavoltage therapy.

TONSIL, FAUCES AND SOFT PALATE (Fig. 5)

In a difficult site surgery appears to have done well. In Cases 41, 42 and 45 excision was carried out by surgical diathermy. Case 42 illustrates another facet of the behavior of this tumor. Following radiotherapy the tumor regressed to a small residue, and although then classed as recurrent, was in fact static when the residue was removed by diathermy. This behavior after high dose therapy is not uncommon and more recently in patients who have not had surgical intervention on account of age, inaccessibility, etc. it has been found that such residues may remain static and symptom free for many years. This is a useful point, particularly in the elderly or in patients already known to have metastases. The 2 cases with combined treatments have again done well.

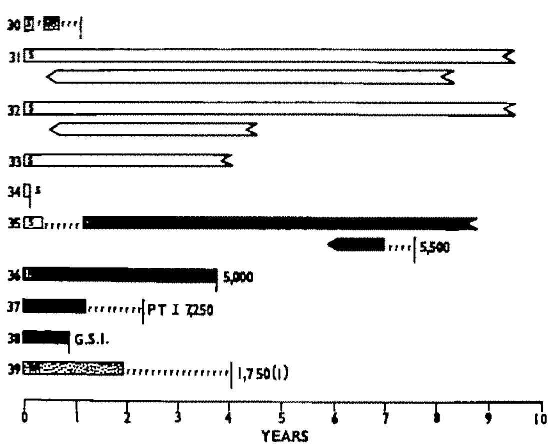


FIG. 4. Cylindroma of tongue and of floor of mouth. PT I=Tongue-pterygoid implant. G.S.I.=Radon seed implant.

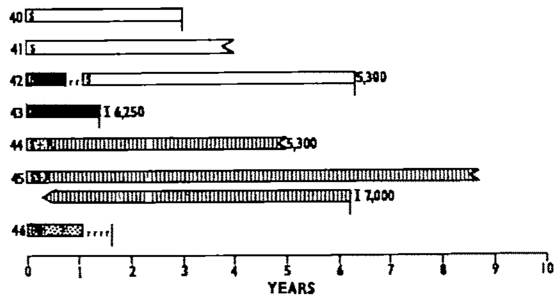


FIG. 5. Cylindroma of tonsil, fauces and soft palate. I=Radon implant.

UPPER ALVEOLUS AND PALATE (ANTRUM CLEAR) (Fig. 6)

Results here by comparison with other sites are so good that one suspects that the nature of the tumor is different. Although all these cases have been reviewed and classed as adenocystic carcinoma, it is interesting that there was some dubiety amongst the histologists regarding cases marked*.

UPPER ALVEOLUS, PALATE AND ANTRUM (Fig. 7)

With invasion of the antrum the prognosis is much worse. The tumor is not readily accessible to surgery, and in retrospect local implantation by antral tube did not cover an adequate volume. Case 63 may be somewhat misleading, in that a tumor of unknown histology was excised in 1938, and it was only on recurrence 13 years later that the histologic diagnosis of adenocystic carcinoma was established. Radical surgery with immediate implantation to the cavity was attempted, but the patient died of postoperative hemorrhage.

A further feature of this tumor is its tendency to spread to the base of the skull, and unless this is prevented by adequate

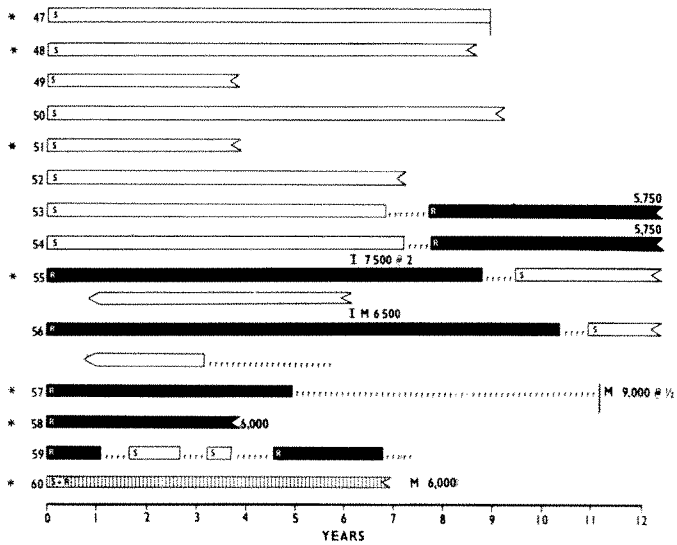


FIG. 6. Cylindroma of upper alveolus and palate (antrum clear). IM = Radium implant plus mold. M = Mold.

treatment initially, the radiotherapist finds himself at a considerable disadvantage due to the low radiation tolerance of adjacent brain. Be the initial treatment a combined treatment, or radiotherapy only, it behooves the radiotherapist to take generous volume to top tolerance dose.

NASOPHARYNX (Fig. 8)

Inaccessible to the surgeon, this remains a problem to the radiotherapist. In 3 weeks, at 4 mev. quality, mid-brain tolerance for small treatment volumes is of the order of 5,000 rads. The temporal lobes will tolerate rather more, perhaps 5,300 rads, but again the optic nerve will not tolerate much over 5,000 rads. Also the volume to be treated is frequently large, and a compromise must be struck. In some cases illustrated doses tend to be low, and again in Cases 74 and 77 the reason for failure was almost certainly inadequate target volume. Once more it is a case of top dose to generous volume. The outlook is,

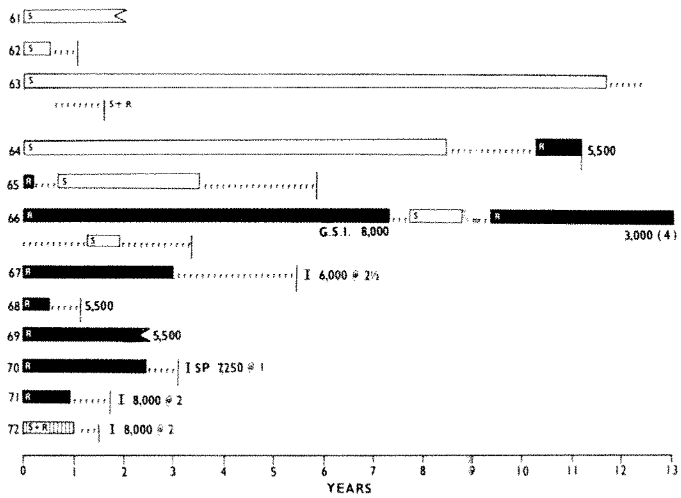


FIG. 7. Cylindroma of upper alveolus, palate and antrum. G. S. I. = Radon seed implant. I SP = Single plane implant. I = Implant by antral tube

however, not entirely bleak. As can be seen, some of these tumors have been controlled from 3 to 5 years.

OTHER SITES (Fig. 9)

In the orbit, surgical exenteration fails because of perineural spread posteriorly. Likewise a local radium implantation as in Case 85 failed. Beam directed therapy controlled Cases 84 and 86 to death, and would appear to be the more appropriate treatment.

Buccal lesions have done well after surgery.

The first tracheal case died postoperatively. The second, Case 92, had 3 attempts at surgical destruction: (1) endoscopic diathermy, (2) thyroidectomy which proved negative, and (3) a repeat of endoscopic diathermy to recurrence—all in the course of 3 months. Thereafter radiotherapy was given and the patient remains well at 7 years.

The larynx case (aged 75 years at time of treatment) remains well at 4 years.

The one case of primary lung cylindroma is interesting. At thoracotomy it was considered inoperable, and biopsy only was performed. Three months after beam directed therapy, a biopsy via the bronchoscope showed degenerating adenocystic carcinoma. A further bronchoscopy over 3 years later was completely negative.

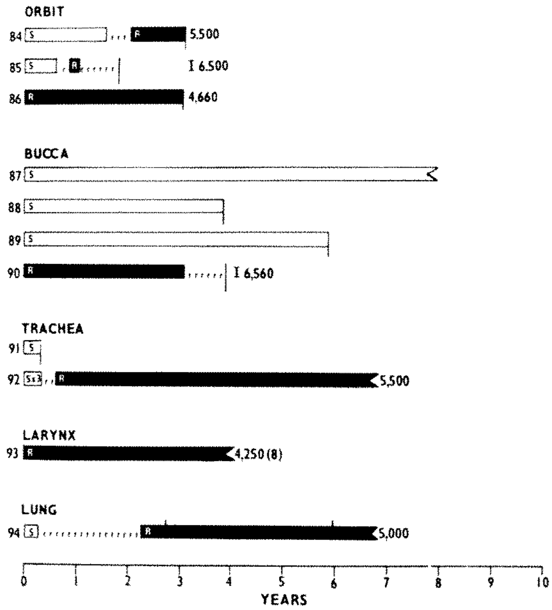


Fig. 9. Cylindroma of orbit, bucca, trachea, larynx and lung. I = Radium implant.

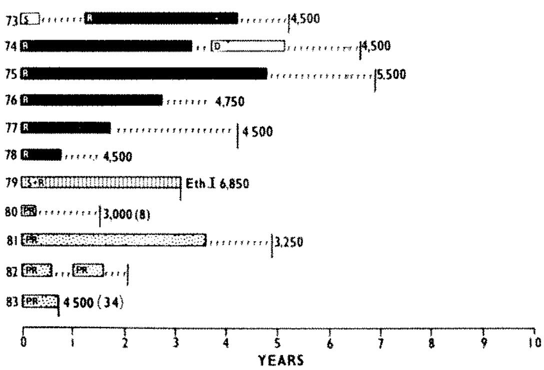


Fig. 8. Cylindroma of nasopharynx. D = Diathermy. Eth. I = Ethmoid implant.

CONCLUSIONS

1. As this tumor may recur at any time up to 30 years, it is inappropriate to talk in terms of cure even when the patient is well to 10 or 15 years. It is better perhaps to think in terms of Primary Control.

2. Although certain authorities have suggested that this tumor is radioresistant, there is no doubt from the evidence presented that primary control can be achieved by radiotherapy. The numbers are too small to define optimal dose and volume, but the results suggest that the target volume must be generous and that the higher doses achieve longer control.

3. Surgery has hitherto been accepted as the initial treatment of choice, but its success may have been limited by the difficulty of obtaining adequate margins of clearance. Radiotherapy does not suffer from this disadvantage to the same extent. Both approaches have their own inherent advantages and are not mutually incompatible. The few combined treatments in this series have been relatively successful and it may be that elective surgery plus radiotherapy should be more fully explored.

4. A large proportion of these patients die from metastases, and if initial treatment has any impact on the incidence of metastases, it might seem wise to try to obtain maximum sterility of the tumor at the earliest opportunity. This again might lead one to elective surgery plus radiotherapy, or even consideration of preoperative radiotherapy. The evidence presented here gives no lead, however, and this must be the subject of a further study.

SUMMARY

An attempt is made to clarify the role of radiotherapy in the management of carcinomas of the salivary glands.

The paper is divided into two sections:
I. Carcinomas of the parotid gland (excluding adenocystic carcinoma).
II. Adenocystic carcinomas of all salivary glands and ectopic sites.

In Section I a comparison is drawn between the poor yet positive salvage of cases already beyond any form of surgery, and the much better results obtained in a group of cases deemed residual following operation, and given radiotherapy immediately postoperatively.

In Section II the management of each of 94 cases of adenocystic carcinoma is illustrated, the cases being grouped according to site of occurrence. Primary control alone is analyzed and the relative merits of surgery and radiotherapy are discussed. From this retrospective analysis, it appears that radiotherapy has made a very positive contribution to the management of these tumors.

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SALIVARY GLAND SCANNING WITH TECHNETIUM 99M PERTECHNETATE*

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TECHNETIUM 99m pertechnetate (TPT) was first introduced as a tracer for brain and thyroid scintillation scanning by Harper *et al.* in 1964.[15] TPT, because of its favorable characteristics, is now widely used for detection and localization of intracranial lesions.[2,11,15,16,23,24,26,31,32,35,36,43] TPT and technetium 99m labeled compounds are also employed in the study of extracranial organs and their pathology.[8,9,15–17,19,23–25,41]

Attempts have been made to localize facial and cervical tumors with counting detectors, using radioiodine labeled tracers,[30,40] phosphorus 32,[14,22,33,39] copper 64 labeled porphyrins[3] and mercury 197 labeled chlormerodrin.[37] Pictorial scans and scintiphoto studies (with a variety of isotopes) have been used to detect and evaluate extracranial head and neck lesions (Table I). Of the agents used, technetium and iodine tracers specifically demonstrate thyroid anatomy. While iodide occasionally outlines the salivary glands and tongue,[34] in our experience only TPT is distributed in a consistently recognizable pattern within these structures.

METHOD

Sialography is frequently used for evaluating salivary gland structure and function.[13,27] Sialograms only give direct information on the status of the duct system, however, and occasionally on the condition of the gland parenchyma. TPT scans, on the other hand, provide a method for studying primarily the parenchyma of the salivary glands. The present report is based on our preliminary experience in evaluating the normal and abnormal salivary glands and their neighboring structures by TPT scanning. Our normal salivary studies have been carried out in concomitance with TPT brain scanning in patients suspected of harboring intracranial pathology. In our pathologic series, patients complaining of "dry mouth" due to non-neoplastic salivary abnormalities or systemic diseases, and patients with neoplasms in or near the salivary glands,

Table I

PICTORIAL ISOTOPE DETECTION OF EXTRACRANIAL HEAD AND NECK LESIONS

Isotope	Tracer Form	Organs and Lesions Evaluated	References
Se^{75}	Methionine	Parathyroid, adenoma	4, 12
Sr^{85}	Chloride	Paget's disease with facial skeleton involvement	21
Tc^{99m}	Pertechnetate	Thyroid	2, 15, 16, 41
I^{123}	Iodide	Thyroid	41
I^{125}	Iodide	Thyroid, carcinoma	5, 6, 10, 29, 41, 42
I^{131}	Iodide	Thyroid, carcinoma, adenoma, cyst, hemorrhage, inflammation	1, 5, 6, 28, 29, 34, 41
I^{131}	Albumin (RISA)	Carcinoma, sarcoma	18
Hg^{197}	Chlormerodrin	Carcinoma, lymphoepithelioma, angiofibroma, sarcoma, "eye tumors"	20, 37, 38

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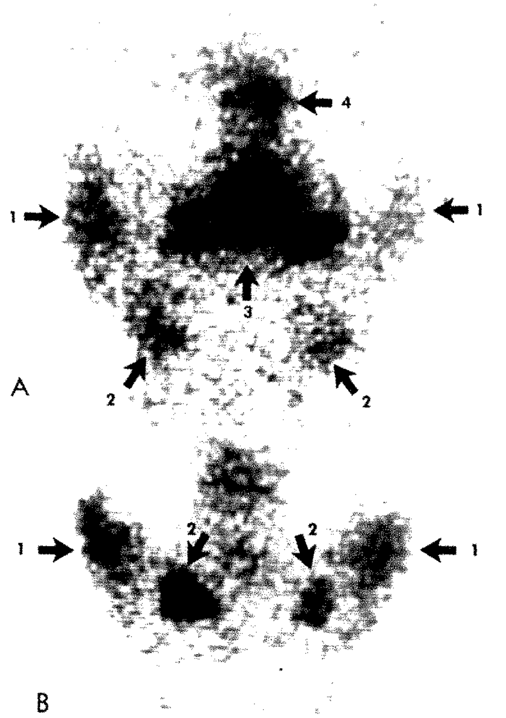

FIG. 1. (*A*) Normal anterior technetium 99m pertechnetate (TPT) salivary scan showing parotid glands (1), submandibular glands (2), oral cavity (3), and nasal cavity (4). (*B*) Normal anterior TPT salivary scan after mouth rinsing. Parotid glands (1) and openings of Stensen's ducts in the mouth (2).

have been evaluated by TPT salivary scanning. In some patients with tumors, multiple scannings with different tracers were carried out in order to help to determine the pathologic diagnosis or the extent of the lesions. In several patients sialography was also carried out.

In most of our adult patients we have used a dose of 1 mc, while only 500 μc are sufficient in younger subjects weighing less than 30 kg. The TPT has been injected intravenously. Thyroid blocking with "cold" iodine, although not really indispensable considering the short half-life and the absence of beta emission by the TPT, has been used in our cases. While thyroid uptake is thus greatly decreased, salivary accumulation is usually not significantly affected. Any of the commercial scanners or fixed devices (cameras) may be used and, considering the 140 kev. energy of the technetium 99m photons, preference should be given to a "low energy" collimator. The choice of the data presentation will depend on the equipment available and the previous experience of the individual investigator. The suggested sequence of the scanning positions is: (1) anterior view, begun about 20 minutes after injection, followed at once by (2) lateral view of the affected side (if the lesion is unilateral), (3)

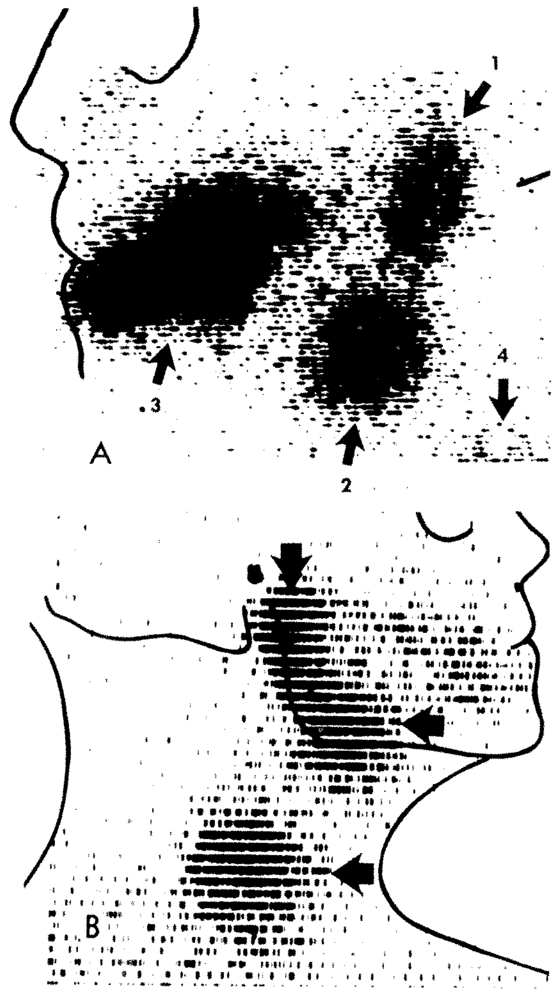

FIG. 2. (*A*) Normal lateral TPT salivary scan showing parotid gland (1), submandibular gland (2), oral cavity (3), and upper pole of thyroid (4). (*B*) Normal lateral TPT salivary scan showing merging outlines of parotid and submandibular glands (upper arrows) and thyroid (lower arrow).

opposite lateral view and (4) posterior view which occasionally is informative. Prominent facial landmarks are marked on the scans for reference.

CLINICAL APPLICATION

TPT scans usually outline the parotid and submandibular glands (Fig. 1, *A* and *B*; and 2, *A* and *B*). Occasionally the sublingual and the palatine glands are demonstrated (Fig. 3). The tongue, the nasopharynx, and the thyroid are also seen in the scans of the salivary "region." Variations in the appearance of the scans among normal patients are common. Significant differences may occur in the amount of TPT accumulated and the size of the salivary glands. A bilateral symmetric decrease in the amount of TPT taken up by the salivary glands is the most common of these variations, and is frequently found in older individuals. Some inequality or asymmetry of the right and left glands is also often demonstrated. Maximum uptake of TPT by the salivary glands occurs between 10 to 60 minutes after injection. Afterwards, serial scans may vary in appearance because the activity in the salivary glands decreases

Fig. 3. Normal lateral TPT salivary scan showing tongue with palatine glands (1) and sublingual glands (2).

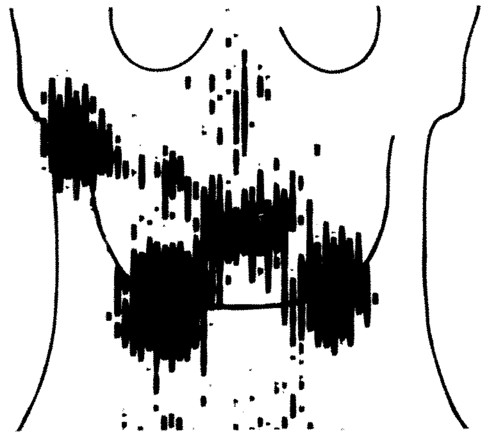

Fig. 4. Scan showing congenital aplasia of the left parotid gland.

progressively, due in part to the physical decay of technetium 99m.

Twenty-nine patients with proven abnormalities of the salivary glands, with systemic diseases known to affect the salivary glands or with extracranial tumors of the head and neck, have been studied by TPT scanning (Tables II and III). Abnormalities in the appearance of the scans were found in 19 patients. Pictorial scanning of the head and neck with TPT is useful for evaluating abnormalities of location, size, and function of the salivary glands and for differentiating among some of the space-occupying lesions which occur within or near these glands. The salivary scan abnormalities which may be of diagnostic value include: (1) decreased salivary TPT accumulation, (2) increased TPT accumulation and (3) salivary defects or displacement.

TPT accumulation by the salivary glands may be less than normal or may be altogether absent. This decrease may be either unilateral or bilateral, depending upon its cause. A unilateral decrease or absence is usually the result of aplasia (Fig. 4), surgical removal, or physical injury, such as irradiation (Fig. 5). A bilateral decrease of TPT uptake is more common and usually is found in patients with Sjögren's syndrome[7] (Fig. 6) or other systemic connective tissue diseases. De-

Table II

NON-NEOPLASTIC ABNORMALITIES—RESULTS OF TECHNETIUM 99M PERTECHNETATE (TPT) SALIVARY SCANNINGS

Diagnosis	TPT Scan*	Remarks
Cystic fibrosis	Normal	No oral complaints
Degenerative arthritis	Normal	a. Sialogram: normal b. Saliva flow: normal
Fibrotic sialadenitis	Normal	Unilateral parotid nodule
Hypogammaglobulinemia	↓ Bilateral	a. Sialogram: normal b. Occasionally dry mouth
Parotid aplasia	↓↓ Left parotid; Normal right parotid	No oral complaints
Psoriatic arthritis	↓↓ Bilateral	Very dry mouth
Radiation injury	↓↓ Right parotid; Normal left parotid	3,000 r to right parotid for suspected lymphoma
Rheumatoid arthritis	↓ Bilateral	No oral complaints
Scleroderma	↓ Left parotid; Normal right parotid	No oral complaints
Sjögren's syndrome	Normal	a. Sialogram: saccular sialectasis (large salivary ducts) b. Slightly dry mouth
Sjögren's syndrome	↓ Bilateral	Slightly dry mouth
Sjögren's syndrome	↓↓ Bilateral	a. Sialogram: punctate sialectasis (small salivary ducts) b. Very dry mouth
Sjögren's syndrome	↓↓ Bilateral	a. Sialogram: sialectasis b. Very dry mouth
Sjögren's syndrome	↓↓ Bilateral	a. Saliva flow: none b. Very dry mouth

* (↓) Slightly decreased salivary uptake.
(↓↓) Greatly decreased uptake or no uptake.

creased TPT accumulation in the salivary glands usually parallels a decrease in saliva flow and a "dry mouth." This decrease in TPT uptake is more frequent in patients with sialectasis of the smaller salivary ducts, as shown by sialography.

Only one primary salivary neoplasm in this series, a Warthin's tumor (papillary lymphoid cystadenoma), clearly concentrated more TPT than normal salivary tissue (Fig. 7). TPT was taken up by one carcinoma, which was also outlined by iodine 131 labeled albumin (RISA) and mercury 197 labeled chlormerodrin. One mixed tumor, despite the fact that it took up no TPT, was well outlined by mercury 197 chlormerodrin.

Five carcinomas and 4 salivary mixed tumors which were scanned were "cold" and accumulated no TPT. Space-occupy-

Table III

EXTRACRANIAL HEAD AND NECK TUMORS—RESULTS OF TECHNETIUM 99M PERTECHNETATE (TPT) SALIVARY SCANNINGS

Tumor	TPT Scan*	Remarks
Carcinoma	+	a. TPT, I^{131}RISA and Hg^{197} chlormerodrin scans: all three visualize tumor b. Sr^{85} scan: outlines bone involved by tumor
Carcinoma	−	TPT scan: parotid defect and displacement
Carcinoma	−	TPT scan: parotid defect and displacement
Carcinoma	Normal	Primary parotid tumor
Carcinoma	Normal	Tumor secondarily involving parotid
Carcinoma	Normal	Tumor secondarily involving parotid
Mixed tumor	−	a. TPT scan: parotid displacement b. Hg^{197} chlormerodrin scan: tracer accumulates in tumor and outlines neoplasm
Mixed tumor	−	TPT scan: parotid defect
Mixed tumor	−	TPT scan: parotid defect
Mixed tumor	Normal	Primary parotid tumor
Warthin's tumor	+	TPT scan: parotid defect and displacement; tumor accumulates more TPT than normal salivary tissue
Carotid body tumor	−	TPT scan: parotid displacement
Lymphosarcoma	−	TPT scan: decreased accumulation of tracer in parotid on side of tumor
Osteosarcoma	Normal	Salivary glands not involved by tumor
Malignant melanoma	Normal	Salivary glands not involved by tumor

* (+) TPT *accumulates* in tumor ("hot" tumor).
(−) TPT does *not* accumulate in tumor ("cold" tumor); salivary gland position or outline is *abnormal.*
(Normal) TPT does *not* accumulate in tumor ("cold" tumor); salivary gland position or outline is *normal.*

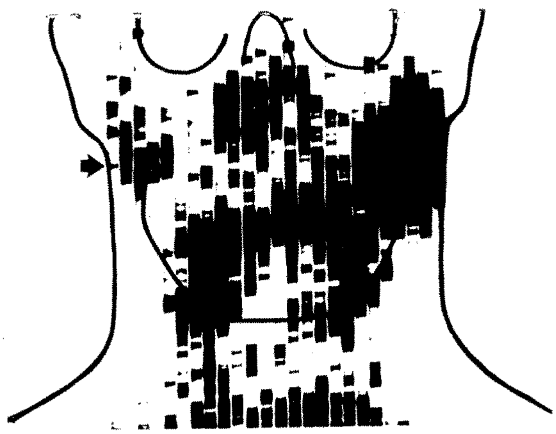

Fig. 5. Scan showing radiation injury to right parotid gland. Decreased TPT uptake (arrow).

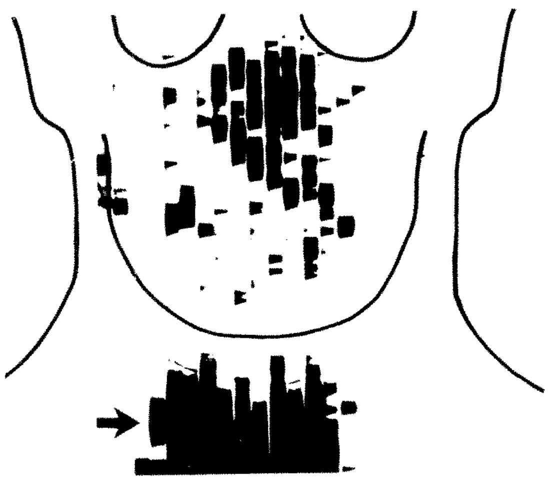

Fig. 6. Scan showing Sjögren's syndrome with very dry mouth. Decreased TPT uptake by all salivary glands. Note normal TPT accumulation by thyroid gland (arrow).

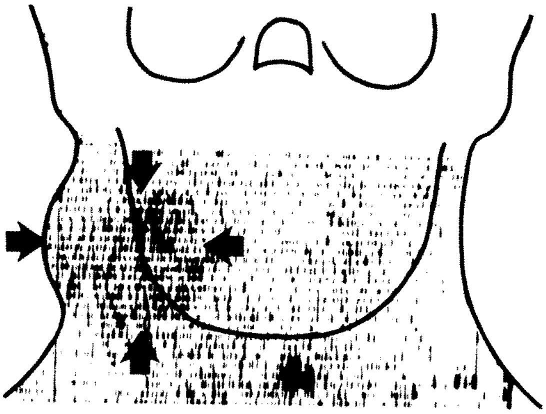

FIG. 7. Scan reveals "hot" Warthin's tumor (arrows). More TPT accumulates in tumor than in normal salivary tissue.

FIG. 8. Scan demonstrates displacement of right parotid and submandibular glands (arrows) by "cold" carcinoma.

ing masses may, however, if of sufficient size and if located within or adjacent to the glands, produce in the scan a salivary gland defect or displacement (Fig. 8). Several "cold" tumors in our series caused such changes in the salivary scans. A "hot" neoplasm, the previously described Warthin's tumor, besides accumulating the TPT, also produced displacement of the tracer-outlined salivary glands.

Finally, another application of salivary gland scanning has been the evaluation of the patency of some cerebrospinal fluid shunts.[11] The rapid demonstration of the salivary glands after TPT injection into ventriculoatrial shunt tubing is an indirect but reliable proof that the shunt is patent.

SUMMARY*

Technetium 99m pertechnetate (TPT) head and neck scans have been used to evaluate patients with a variety of extracranial tumors and non-neoplastic conditions. Decreased saliva flow, a clinically dry mouth and sialectasis of the smaller salivary ducts are associated with a decrease in TPT uptake by the salivary glands. TPT scans are useful for discriminating among different salivary gland tumors (such as "hot" Warthin's tumors and "cold" mixed tumors). The position of the salivary glands can be determined by TPT scanning and the size and extent of adjacent mass lesions can be evaluated.

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HIGH INTENSITY PROXIMITY THERAPY OF INTRAORAL CANCER*

WITH DESCRIPTION OF A NEW AFTER-LOADING UNIT

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CANCER of the oral cavity usually is fatal in about 1 year if not controlled. The disease consists of two parts—the primary growth and the metastatic spread. Each part requires specific therapeutic measures. Destruction of the primary growth merits first consideration and is the subject of this paper. The treatment of lymph node metastasis is not considered, except in a general way.

In the treatment of intraoral cancer the author has used a high intensity divided dose technique, applying radium in close proximity to the tumor surface. In subsequent years over 5 per cent of our patients developed from 1 to 6 additional primary growths in different parts of the mouth, but in this report only data from the first growth are considered.

The American Cancer Society estimates that in the United States 7,000 people will die of intraoral cancer in 1967, so it is evident that we should re-examine our treatment policies. It is the purpose of this article to discuss logic in radiation therapy and to describe a technique which is new to the profession but has been successfully used by the author for many years. In addition a new unit called the Pneumatron is presented. This is an after-loading, remote controlled device which will permit the employment of the technique without exposure to personnel.

The greater sensitivity of some malignant cells over normal cells to ionizing radiations may be more apparent than real, for occasionally an overdose may cause necrosis of the normal tissues and be followed by re-growth of the malignant tumor. It is therefore evident that much of the host resistance to tumors lies in the tumor bed. In recent months experimental work has been done on the natural defenses against tumor growth with emphasis upon antibody formation.

The significance of the tumor bed is illustrated by the difficulty in destroying a malignant growth when that growth is in bone or invades the periosteum of the bone. In these sites radiosensitive growths may be destroyed but resistant tumors tend to recur after treatment. This clinical finding may be, in part, explained by the recent work on the hyperbaric oxygenation of tumors during irradiation, suggesting that oxygen in the tumor increases its sensitivity to irradiation.

RADIATION THERAPY

Ralston Paterson[6] has stated in his book: "The radium applicator (surface) is in many senses the only ideal method (of radiation therapy) in that where applicable it enables radiation to be given without trauma to a zone of tissue almost exactly limited to the tumor-bearing zone." He further states[7] that "In the treatment of cancer of the mouth, radiation treatment is to be preferred to surgical treatment (including diathermy) as the first treatment in all sites and whether the growth be early or late." Sir Stanford Cade,[8] expresses essentially the same opinion in his four volume work "Malignant Disease." In the past few years American radiotherapists have taken a more active role in the treatment of intraoral cancers. Some patients with mouth cancer, particularly those with cervical metastasis, require the cooperation of both an experienced radiotherapist and

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TABLE I

TOTAL NO. OF PATIENTS

Site	No.
Tongue	139
Floor of mouth	43
Tonsil (+pillar+R.M.T.*)	66
Gingiva	39
Buccal mucosa	46
Palate	11
Total	344

* R.M.T.=retromolar trigone.

an experienced head and neck cancer surgeon.

The discovery of radium in 1898 provided an ideal agent with which to treat intraoral tumors. Its gamma rays applied in close proximity to a growth provide destructive irradiation to the tumor and still permit protection of the tumor bed and adjacent structures through the mechanism of the inverse square law. Since radium was very costly, therapeutic techniques were initially built around small sources. Thus intraoral cancers were treated either by needle implantation or from the surface by means of a mold in which small sources were dispersed strategically throughout the mold. The implantation of radium needles is traumatic and painful, requires not only a knowledge of irradiation but also a certain amount of surgical dexterity. Both radiation implantation and the preparation and application of a mold must be meticulously done, and results in a certain amount of radiation exposure to the physician as well as to the paramedical personnel.

In the past few years great emphasis has been placed upon high energy radiation. With external beam therapy it is now possible to deliver a predetermined dose to any part of the body. The real problem, however, is not to deliver a set dose, but to destroy the cancer and at the same time to spare the normal tissues. Since the radiosensitivity of both tumors and normal tissues differs in every patient and since at times the difference is not very great, it is unavoidable that a uniform dose to a block of tissue may produce serious injury to normal structures within the treated area. In the treatment of intraoral cancer with high energy external irradiation, Fletcher and Lindberg[4] have reported injury to the mandible in 37.5 per cent of the patients, in addition to soft tissue complications.

This paper is based upon the treatment of 344 patients with cancer of the oral cavity treated personally by the author over a period of 33 years. All were epidermoid growths with the exception of 4 lymphosarcomas of the tonsil, 1 myosarcoma of the tongue and 1 metastatic hypernephroma in the cheek. Included are 139 patients with tongue cancer, 43 patients with cancer of the floor of the mouth, 66 patients with cancer of the tonsil, 39 patients with cancer of the gingiva, 46 patients with cancer of the buccal mucosa and 11 patients with cancer of the palate (Table 1).

METHOD

In 1917 my predecessor, Dr. Frank E. Simpson, purchased 1.5 grams of radium which was placed in an emanation plant built by Failla. Through trial and error Simpson devised a high intensity divided dose technique, modifications of which form the background of our method, which is as follows:

The radium applicator is a small metal box $1.5\times2\times0.5$ cm. in size. Rubber tubing 4 mm. in thickness covers the applicator, which is fixed to the end of a stiff aluminum rod 1 meter in length. It is then loaded with 400 to 600 mg. of radium and covered with a sterile finger cot. Figure 1 is the chart of the isodose curves around the face of a 300 mc cobalt 60 applicator measuring $2\times1\times0.5$ cm. which is equivalent to the radium applicator in size and strength. With a covering of 4 mm. of rubber, a dose of 100 r/min. is delivered at the surface of the

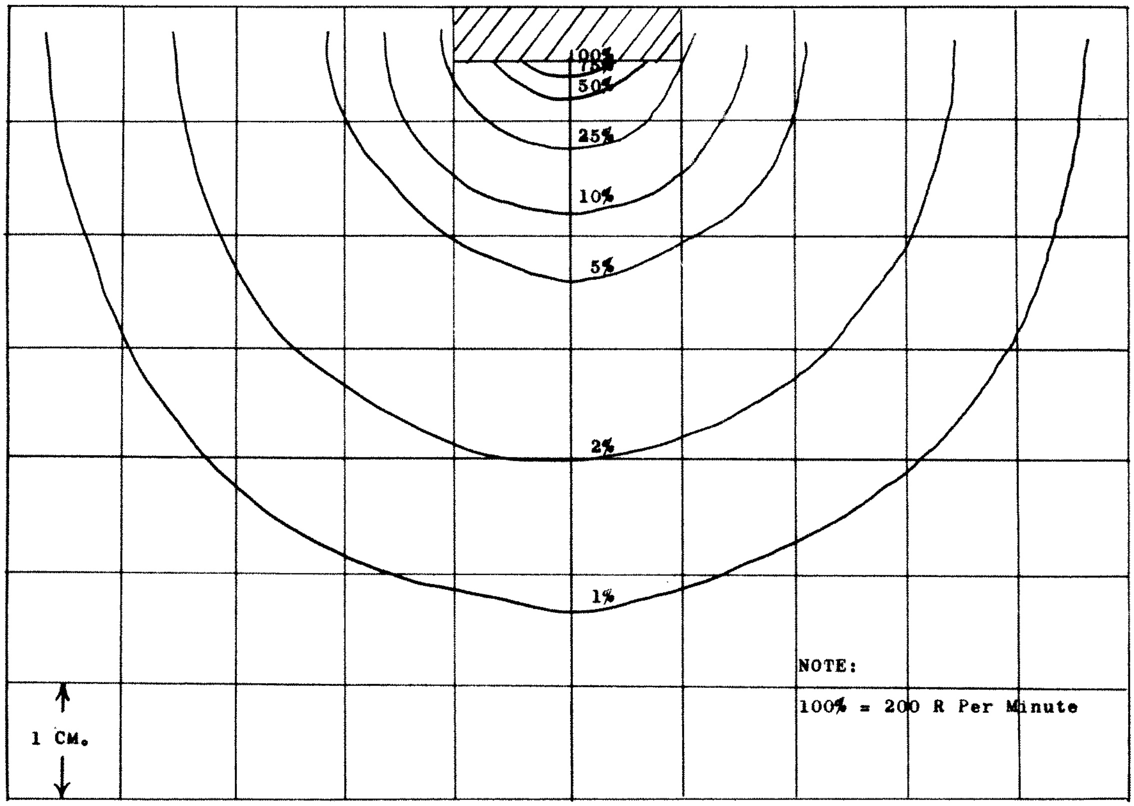

Fig. 1. Isodose curves for 300 mc cobalt 60 applicator. The 100% dose represents 200 r per minute and the distance between the lines is 1 cm. both vertically and horizontally.

covered applicator. One centimeter below the surface the dose rate is 20 r/min., and 2 cm. into the tissue the dose rate is approximately 8 r/min. This rapid fall-off protects the tumor bed from serious injury.

The patient is seated on a stool adjusted so that his head is nearly encircled by a 2 inch thick lead collar fixed to the wall of the treatment room (Fig. 2). A 4 inch thick lead block is adjusted in front of the patient. The operator standing behind an additional movable shield composed of 2 inches of steel and 1 inch of lead is protected by a total of 5 inches of lead and 2 inches of steel. A bell shaped lead guard is affixed to the end of the aluminum rod to protect the operator's hands. The applicator is held over the periphery of the tumor covering different portions in 10 minute daily treatments. A dose of 6,000 to 8,000 r is delivered to all portions of the tumor over a 2 to 4 week period.

After each intraoral treatment, the lymph node bearing area on the side of the lesion is treated with a radium pack containing 200 to 800 mg. of radium at a distance varying from 2 to 4 cm. from the skin. A total dose of about 6,000 r to the skin surface is usually administered over a period of 4 to 6 weeks. The purpose of these treatments is to prevent the development of metastatic tumor or, in case that enlarged lymph nodes are already present, to cause them to shrink or to disappear. This procedure holds further growth in abeyance until the destruction of the primary lesion is assured. If palpable lymph nodes have been found at any time, the patient is referred for a radical neck dissection. Prophylactic dissections are not advocated.

Since the muscle fibers of the tongue run in all planes, including the vertical, and since cancer extends between the muscle

Fig. 2. Present technique. The patient's head is surrounded by a lead collar. There is a thick lead block adjusted before the patient.

fibers, it is usual for tongue cancer to deeply invade the organ. It is difficult to deliver an adequate dose to the deeper parts of infiltrated lesions by proximity therapy alone, although the superficial part of the tumor is destroyed and the residuum shrunk to small proportions. The persistent part of the growth is then implanted with gold radon seeds of 0.5 mc strength, which are inserted 2 at a time in tandem, 1 being deposited in the tumor bed below the tumor and 1 in the deeper portions of the residual mass. Paterson's implantation schemes are used. Of our 139 patients with tongue cancer 99 were implanted. Of the 40 not implanted, 12 were not treated or had discontinued treatment, 16 were late Stage IV patients treated for palliation only, and 12 had superficial growths that did not require implantation. Implants were inserted in 10 other patients; 8 had advanced tonsillar fossa and pillar tumors in which the tumor had crossed the glossopalatine space and involved the adjacent portion of the tongue.

ADVANTAGES OF THE METHOD

The required dose may be delivered to a tumor with little danger of serious injury to the tumor bed or to adjacent structures. The removal of teeth is not required. Hospitalization is unnecessary and the patient begins to feel better after the first few treatments. The cure rate of the primary growth is quite satisfactory.

MATERIAL

Of our 344 patients 275 were men and 69 women, a ratio of about 4 to 1 (Table II). The youngest patient was a man 26 years

Table II

SEX

Site	Male	Female
Tongue	108	31
Floor of mouth	36	7
Tonsil (+pillar+R.M.T.*)	52	14
Gingiva	32	7
Buccal mucosa	38	8
Palate	9	2
Total	275	69

* R.M.T. = retromolar trigone.

of age with tongue cancer. The oldest, also a man, aged 89 years, had a growth in the floor of his mouth. The mean age was highest for cancer of the gingiva and was 65 years. The lowest mean age of 50 years was found in cancer of the palate (Table III). The TNM stages of all patients are disclosed in Tables IV to IX. Ninety-three primary tumors were Stage T_1, 86 Stage T_2, 55 Stage T_3, and 110 Stage T_4 (Table X).

TABLE III

AGE

Site	Youngest	Oldest	Average	Mean
Tongue	26	88	60	59
Floor of mouth	42	89	63.8	62
Tonsil (+pillar +R.M.T.*)	30	83	61	62
Gingiva	32	87	65	65
Buccal mucosa	33	83	64	61
Palate	38	72	45	50

* R.M.T. = retromolar trigone.

RESULTS

Head and neck cancers present two separate but related problems, the treatment of the primary tumor and the treatment of the metastatic lesions in the cervical lymph nodes. In general the treatment of the former is radiologic and of the latter surgical. As long as viable cells exist in the primary tumor it is useless to remove evident metastases. Although some of our patients died of uncontrolled metastases, complete destruction of the primary tumor was assumed if a patient lived one or more years without evidence of persistent disease.

In addition to indicating the staging of both the primary growth and the lymph node metastasis, Tables IV to IX present the percentage of destruction of the primary growths in the treated cases. Since patients with T_4 tumors are frequently treated for palliation only, the best test of a technique for the destruction of tumors is the results obtained in $T_1+T_2+T_3$ tumors.

A detailed report on tongue cancer made in 1957 disclosed a 30.9 per cent 5 year survival rate with the patients free of disease.[1]

Table IV shows that the primary tongue cancer was destroyed in 85.3 per cent of T_1, 64.5 per cent of T_2, 56.0 per cent of T_3 and 29.0 per cent of T_4 tumors. Of the 81 patients in $T_1+T_2+T_3$ groups, the primary tumor was destroyed in 58 patients (71.5 per cent).

TABLE IV

TONGUE

TNM Stages

Stage	N_0	N_1	N_2	N_3	Total	Not Treated	Treated	Primary Tumor Destroyed	Per Cent Destroyed
T_1	32	3	4	0	39	5	34	29	85.3
T_2	19	10	3	1	33	2	31	20	64.5
T_3	4	9	5	1	19	3	16	9	56.0
T_4	8	10	17	13	48	10	38	10	29.0
Total	63	32	29	15	139	20	119	68	57.0

$T_1+T_2+T_3$ = Destroyed 58 of 81 (71.5 per cent).

Table V

FLOOR OF MOUTH

TNM Stages

Stage	N_0	N_1	N_2	N_3	Total	Not Treated	Treated	Primary Tumor Destroyed	Per Cent Destroyed
T_1	9	1	0	1	11	0	11	10	91.0
T_2	5	2	1	0	8	0	8	7	87.0
T_3	4	2	0	2	8	1	7	6	85.7
T_4	3	1	4	8	16	0	16	2	12.5
Total	21	6	5	11	43	1	42	25	59.5

$T_1+T_2+T_3$= Destroyed 23 of 26 (88.5 per cent).

Table v discloses that in cancer of the floor of the mouth, 91.0 per cent of T_1, 87.0 per cent of T_2, 85.7 per cent of T_3 and 12.5 per cent of T_4 tumors were destroyed. The destruction rate in Stages $T_1+T_2+T_3$ was 88.5 per cent or 23 of 26 patients.

Table vi presents the results in buccal carcinoma. The primary tumor destruction rate in T_1 was 94.4 per cent, T_2 70.0 per cent, T_3 50.0 per cent, and T_4 12.5 per cent. The rate in patients with $T_1+T_2+T_3$ tumors was 80.0 per cent, or 28 of 35 patients. In buccal cancer intraoral therapy is supplemented with an additional 1,000 to 2,000 r by radium pack treatments from the skin surface. In 1952 a 5 year cancer free survival rate of 35.7 per cent was reported for all cases. Favorable cases (without metastasis, periosteal involvement or previous treatment) showed a 5 year survival rate of 76.4 per cent.

Table vii records the results in cancers located in the tonsillar fossa, the anterior pillar and the retromolar trigone. Tumors in these three areas are grouped together, since moderately advanced tumors in any one area soon spread to one or both of the other sites. In treated cases destruction of the growth was obtained in 83.3 per cent of T_1, 77.0 per cent of T_2, 37.5 per cent of

Table VI

BUCCAL MUCOSA

TNM Stages

Stage	N_0	N_1	N_2	N_3	Total	Not Treated	Treated	Primary Tumor Destroyed	Per Cent Destroyed
T_1	17	0	1	0	18	0	18	17	94.4
T_2	8	5	1	0	14	1	13	9	70.0
T_3	1	1	3	0	5	1	4	2	50.0
T_4	2	3	2	2	9	1	8	1	12.5
Total	28	9	7	2	46	3	43	29	67.7

$T_1+T_2+T_3$= Destroyed 28 of 35 (80.0 per cent).

Table VII

TONSIL (+PILLAR+R.M.T.*)
TNM Stages

Stage	N_0	N_1	N_2	N_3	Total	Not Treated	Treated	Primary Tumor Destroyed	Per Cent Destroyed
T_1	6	0	0	1	7	1	6	5	83.3
T_2	5	3	2	4	14	1	13	10	77.0
T_3	5	5	5	4	19	3	16	6	37.5
T_4	4	6	9	7	26	9	17	6	35.3
Total	20	14	16	16	66	14	52	27	52.0

* R.M.T. = retromolar trigone.
$T_1+T_2+T_3$ = Destroyed 21 of 35 (60.0 per cent).

T_3 and 35.3 per cent of T_4 tumors. Combining $T_1+T_2+T_3$ tumors, 21 of 35 or 60.0 per cent were destroyed.

Table VIII presents the results in gingival cancers. Here the results are poorer due to an absence of a good tumor bed. Of 39 tumors, 14 were in the upper jaw and 25 in the lower jaw. No upper jaw gingival tumors were controlled. The rate of destruction for lower jaw gingival tumors was 85.7 per cent of T_1, 20.0 per cent of T_2, and no controls were recorded in T_3 or T_4 tumors. The destruction rate of $T_1+T_2+T_3$ mandibular gingival tumors was 47.0 per cent. It is our policy to treat gingival tumors with one course of definitive therapy. If destruction of the growth does not result, the tumor at least has been made much smaller and surgical removal is then advised.

Table IX shows good results in early palate tumors. Six of our 11 patients had growths over the hard palate, 4 in the soft palate and 1 in both. All patients with Stage T_1 and T_2 cancers recovered, while the 2 with Stage T_3 and T_4 succumbed. The cancer destruction rate in Stages $T_1+T_2+T_3$ was 90.0 per cent or 9 of 10 patients.

Table X presents the total staging of all patients and Table XI the percentage of primary tumor destruction in all areas.

DISCUSSION

Liversage[5] recently presented a review of experimental work on the effectiveness of high intensity dosage in comparison with low intensity dosage. He also considered the effect of dividing the dose, and variations in the over-all treatment time. Although reasoning primarily from a theoretic viewpoint, he concludes that in the treatment of cancer of the cervix greater injury is done to rapidly dividing cells with a high intensity technique than to cells with a longer period between cell division episodes. He believes that the treatment should be divided into at least 6 separate doses and spread over a period of at least 3 weeks.

Our experience confirms the efficiency of a high intensity divided dose technique with the element in close proximity to a primary intraoral tumor. The same technique has been used successfully in accessible tumors in many areas, including the lip, the skin in general, the cervix and in Stage T_1 carcinoma of the vocal cords.

PNEUMATRON

Realizing the logic of a high intensity divided dose therapy at short distance, physicians of the Charing Cross Hospital

TABLE VIII

GINGIVA
TNM Stages

Stage	N_0	N_1	N_2	N_3	Total	Not Treated	Treated	Primary Tumor Destroyed	Per Cent Destroyed
T_1	Max. 2 Man. 6	Max. Man. 2	Max. Man.	Max. Man.	Max. 2 Man. 8	Max. Man. 1	Max. 2 Man. 7	Max. 0 Man. 6	Max. 0 Man. 85.7
T_2	Max. 3 Man. 9	Max. Man. 2	Max. Man.	Max. 1 Man. 1	Max. 4 Man. 12	Max. 1 Man. 2	Max. 3 Man. 10	Max. 0 Man. 2	Max. 0 Man. 20.0
T_3	Max. 3 Man.	Max. Man.	Max. Man.	Max. Man.	Max. 3 Man.	Max. 1 Man.	Max. 2 Man.	Max. 0 Man. 0	Max. 0 Man. 0
T_4	Max. 3 Man. 1	Max. 2 Man. 2	Max. Man. 1	Max. Man. 1	Max. 5 Man. 5	Max. 2 Man. 1	Max. 3 Man. 4	Max. 0 Man. 0	Max. 0 Man. 0
Totals	Max. 11 Man. 16	Max. 2 Man. 6	Max. 0 Man. 1	Max. 1 Man. 2	Max. 14 Man. 25	Max. 4 Man. 4	Max. 10 Man. 21	Max. 0 Man. 8	Max. 0 Man. 38.0

Maxilla – $T_1+T_2+T_3$ = Destroyed none of 10.
Mandible – $T_1+T_2+T_3$ = Destroyed 8 of 17 (47.0 per cent).

TABLE IX

PALATE
TNM Stages

Stage	N_0	N_1	N_2	N_3	Total	Not Treated	Treated	Primary Tumor Destroyed	Per Cent Destroyed
T_1	7	0	0	1	8	0	8	8	100.0
T_2	1	0	0	0	1	0	1	1	100.0
T_3	0	1	0	0	1	0	1	0	0
T_4	0	1	0	0	1	0	1	0	0
Total	8	2	0	1	11	0	11	9	81.8

$T_1+T_2+T_3$ = Destroyed 9 of 10 (90.0 per cent).

TABLE X

TNM STAGES OF ALL PRIMARY GROWTHS

Site	T_1 Stage	T_2 Stage	T_3 Stage	T_4 Stage	Total
Tongue	39	33	19	48	139
Floor of mouth	11	8	8	16	43
Tonsil (+pillar+R.M.T.*)	7	14	19	26	66
Gingiva	10	16	3	10	39
Buccal mucosa	18	14	5	9	46
Palate	8	1	1	1	11
Total	93	86	55	110	344

* R.M.T. = retromolar trigone.

TABLE XI

SUMMARY OF DESTRUCTION RATE

Site	Total	Not Treated	Treated	Primary Tumor Destroyed	Per Cent Destroyed	Per Cent Destroyed $T_1+T_2+T_3$
Tongue	139	20	119	68	57.0	71.5
Floor of mouth	43	1	42	25	59.5	88.5
Buccal mucosa	46	3	43	29	67.7	80.0
Tonsil (+pillar+R.M.T.*)	66	14	52	27	52.0	60.0
Gingiva: Maxilla / Mandible	14 / 25	4 / 4	10 / 21	0 / 8	0 / 38.0	0 / 46.5
Palate	11	0	11	9	81.8	90.0
Total	344	46	298	166	57.6	70.0

* R.M.T. = retromolar trigone.

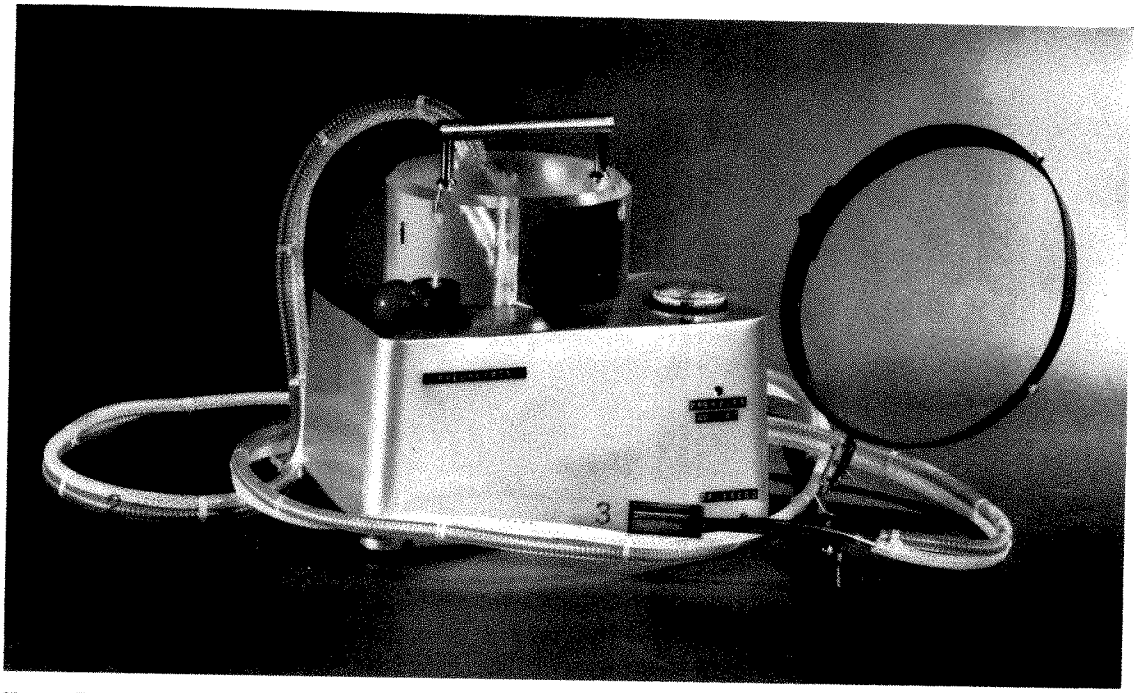

Fig. 3. Pneumatron, a remote controlled, pneumatic after-loading device. 1. Solid plastic cylinder representing tungsten well for cobalt 60 storage. 2. Steel reinforced plastic tubing for pneumatic transfer of sources. 3. Intraoral applicator. 4. Air flow control valve. 5. Air pressure gauge. 6. Source release lever.

in London, of the Radiumhemmet in Stockholm and of the Memorial Hospital in New York are experimenting with after-loading units either using cobalt 60 or cesium 137. The English call their experimental model the "Cathetron." Their sources are forced through a catheter at the end of a wire. At this time their unit is being used experimentally only in cancer of the uterus.

We have devised an after-loading remote controlled unit using cobalt 60 pellets. Since our unit transfers the sources by pneumatic pressure the name "Pneumatron" seems appropriate. The unit eventually will be used for the treatment of accessible tumors in any site, but because of the great need for general usage of the technique in intraoral tumors it will be used first in this area.

The unit (Fig. 3) consists of a tungsten alloy reservoir 6 inches in diameter in which the sources will be kept when not in use, an applicator which is fixed in the mouth against the surface of the tumor, and a tube connecting the reservoir with the applicator. In the initial unit the sources consist of 10 stainless steel balls $\frac{1}{8}$ inch in diameter with 7 mg. of cobalt 60 in the center. Round sources were suggested to the author by Herbert M. Parker. The cobalt 60 has a specific activity of 14.3 curies per gram. Each ball has essentially the equivalent of 100 mg. of radium in irradiating power, so that the 10 small sources equal 1 gram of radium. The balls are transferred to and from the applicator by pneumatic pressure, through a flexible plastic tube reinforced with steel wire.

The applicator measures $3\times1\frac{1}{2}\times1\frac{1}{2}$ cm. in size. Two tubes enter at one end, one large enough to permit the passage of the sources into the applicator and one smaller for the return flow of air. The larger tube lies in the center of the applicator with its center 8 mm. from the surface of the unit. The back half of the applicator is composed of tungsten to provide relative protection

to tissue opposite the cancer. The rest of the applicator is plastic with 1 mm. soft rubber across the face.

The applicator is fixed and held in place by a headband with an adjustable but rigid arm which comes down anterior to the mouth. It is possible to adjust the applicator to any part of the mouth or pharynx (Fig. 4).

The mouth and pharynx are anesthetized with 0.5 per cent dyclonine hydrochloride and the applicator adjusted. The operator leaves the room, going to a control panel. The sources are then transferred to the applicator where they remain from 3 to 5 minutes. During the treatment the patient is kept under constant observation through a lead glass window. The air flow is then reversed and the sources are returned to the reservoir.

It is anticipated that many different shapes and sizes of applicators will be devised as the use of the Pneumatron is extended to the treatment of accessible tumors in other areas. The number of radioactive sources also will be increased as need arises.

SUMMARY

The treatment of intraoral cancer is composed of two related but separate parts; *i.e.*, the treatment of the primary tumor (a radiologic problem) and the treatment of metastatic lymph nodes (a surgical problem). In this paper only definitive treatment of the primary growth is considered.

The technique used in the 344 patients reported consisted of holding a 500 mg. radium applicator against the surface of the growth for 10 minutes daily, until a dose of about 8,000 r had been delivered to all parts of the tumor. Associated lymph node enlargements were concurrently treated with a radium pack at a distance of 2 to 4 cm. using 400 to 800 mg. of radium for 40 minutes at each treatment. After destruction of the primary tumor is assured, the patient is referred for block dissection of the lymph nodes.

Tables presented disclose the destruction rate of all tumors in different stages and locations. The average rate was 70.0 per cent for Stage T_1, plus T_2, plus T_3 tumors.

Since the handling of powerful radium applicators cannot be properly supervised

Fig. 4. Applicator in treatment position.

in most treatment centers, a new after-loading, remote controlled unit called the "Pneumatron" has been developed. This unit permits the after-loading of a pre-adjusted applicator with cobalt 60 pellets in the center of stainless steel balls. These balls are transferred from the reservoir to the applicator and returned by pneumatic pressure.

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INTEGRATED IRRADIATION AND OPERATION IN TREATMENT OF CANCER OF THE LARYNX AND HYPOPHARYNX*

A PRELIMINARY REPORT

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FOR the past 4 years we have employed a program of combined irradiation and operation in all suitable patients with primary carcinoma of the larynx and hypopharynx. All patients, not previously treated, with Stage II lesions or greater, physically able to tolerate irradiation and operation, were accepted for integrated therapy. This paper concerns the early results of this program.

CLINICAL MATERIAL

From July 1962 until March 1967, 75 patients with carcinoma of the larynx and hypopharynx were seen. Thirteen patients had recurrent lesions following previous therapy. Of the 62 patients with primary untreated lesions 47 had carcinoma of the larynx and 15 of the hypopharynx (Table I). The patients were examined by a radiotherapist and surgeon at the first visit and the lesion was staged by one of us (R.G.).

TABLE I

DISPOSITION OF PATIENTS WITH PRIMARY UNTREATED LESIONS OF LARYNX AND HYPOPHARYNX

Primary Untreated Lesions of Larynx	47
Candidates for Palliation Only	15
Candidates for Treatment	32
Radiation therapy only	3
Surgery only	2
Refused operation, treated with irradiation	4
Refused all therapy	2
Combined Therapy	21
Primary Untreated Lesions of Hypopharynx	15
Candidates for Palliation Only	10
Radiation therapy	7
Chemotherapy	2
Died during work-up	1
Combined Therapy	5

The majority of our patients came from a rural Appalachian setting. They had a fatalistic outlook and poor access to medical care; thus most of the primary lesions seen were moderately to far advanced (Table II). Only 4 per cent of the laryngeal lesions were in clinical Stage I compared to the incidence of 56 per cent for this stage reported by the American Joint Committee on Cancer Staging and End Results.[2]

Because of the advanced stage of disease encountered and the not infrequent refusal of therapy, only 31 of 62 patients received therapy. Twenty-six of this group had combined therapy and 3 of these are too early postoperative to evaluate. Of the 23 patients evaluated, one-third were in each of 3 clinical stages—Stage II, III and IV (Table III). Patients classified as Stage II because of no palpable lymph nodes often had very large primary lesions; 3 of these involved the skin of the neck including 1 with multiple salivary fistulae.

RADIATION THERAPY

All patients received a tumor dose of 5,000 to 6,000 rads of cobalt 60 radiotherapy delivered through bilateral opposed ports. Port size averaged 6×10 cm. and was adjusted to cover the palpable lymph nodes when these were present. The period of treatment was 5 to 6 weeks.

* Presented at the Forty-ninth Annual Meeting of the American Radium Society, Toronto, Ontario, Canada, May 29–31, 1967.
Part of Panel Symposium: Head and Neck Cancer. Moderator, Richard H. Jesse, M.D., Houston, Texas.
From the Department of Radiology, Section of Radiotherapy; and the Department of Surgery, Section of Oncology, University of Kentucky Medical Center, Lexington, Kentucky.
Supported in part by a Grant from the American Cancer Society, Kentucky Division.

Table II

CLINICAL STAGING* OF ALL PRIMARY LESIONS

(62 Patients)

Stage	Larynx (47)		Hypopharynx (15)		Total (62)	
	No.	Per cent	No.	Per cent	No.	Per cent
I	2	4	0	0	2	3
II	16	34	3	20	19	31
III	12	26	4	27	16	26
IV	16	34	7	47	23	37
Unstaged	1	2	1	7	2	3

* American Joint Committee on Cancer Staging and End Results Reporting.

Table III

STAGE OF OPERATED LESIONS

(23 Patients)

Stage	Larynx (18)		Hypopharynx (5)		Total (23)	
	No.	Per cent	No.	Per cent	No.	Per cent
I	0	0	0	0	0	0
II	6	33	2	40	8	35
III	6	33	2	40	8	35
IV	6	33	1	20	7	30

OPERATIVE THERAPY

Patients were brought to operation on an average of 6 weeks after irradiation. Radical neck dissection accompanied laryngectomy on the major side of the lesion whether lymph nodes were palpable or not. In 3 instances of midline lesions without palpable lymph nodes, laryngectomy alone was performed. Bilateral radical neck dissection was done only when enlarged lymph nodes were present in the contralateral neck prior to radiation therapy (Table IV).

The skin incision at operation was always made outside the area of the radiation ports. Radical laryngectomy was performed through a transverse incision in the lower neck. Laryngectomy and radical neck dissection were done through a hockey stick shaped incision;[1] when bilateral neck dissection was done this incision was extended to form a U.

Table IV

OPERATIONS

Laryngectomy only	3
Laryngectomy and Radical Neck Dissection	13
Laryngectomy and Bilateral Radical Neck Dissection	7

There were no operative deaths. Six patients (25 per cent) developed salivary fistulae. Four closed spontaneously. One required secondary closure. One was accompanied by carotid artery rupture which was ligated without sequelae although the fistulae subsequently closed spontaneously (Table V). Previous irradiation did not appear to affect blood loss at operation or length of hospital stay (Table VI).

RESULTS

In 3 of the 23 operated patients, no

Table V

POSTOPERATIVE COMPLICATIONS—23 PATIENTS

Salivary Fistulae—Closed Spontaneously	4
Postoperative Hematoma under Flap	1
Sponge Left Under Flap	1
Salivary Fistula Requiring Secondary Closure	1
Salivary Fistula-Carotid Rupture—Ligated without Sequelae	1
Total	8

Table VI

AVERAGE BLOOD REPLACEMENT AND AVERAGE HOSPITAL STAY

Type of Operation	Blood (cc.)	Hospital Stay
Laryngectomy	0	10 Days
Laryngectomy and Radical Neck Dissection	770	*19 Days
Laryngectomy and Bilateral Radical Neck Dissection	1,500	23 Days

* Omitting one patient in hospital several months because of disposition problems.

Table VIII

SURVIVAL ANALYSIS BY LIFE TABLE METHOD

	12 Mo.	24 Mo.	36 Mo.
Total No.	17	8	3
Alive	16*	7*	3
Dead	1	1	0
Per Cent Survival	94.1	87.5	100

* One patient alive with recurrent cancer.

trace of residual tumor could be found in either the primary site or in the lymph nodes. Five of the primary tumors showed complete regression and 17 showed some evidence of radiation effect. In 12 patients with palpable lymph nodes prior to irradiation, only 4 had evidence of tumor in the lymph nodes at operation. This is a higher number of false positives than ordinarily found and is assumed to be due to preoperative irradiation (Table VII).

Survival of treated patients was analyzed by the life table method (Table VIII). Of those surviving 3 years no tumor recurrence was present; of the 2 year survivals 1 had recurrent disease, and of the 1 year survivals 1 had cancer present. Because of the small group involved, laryngeal and hypopharyngeal patients are listed together.

DISCUSSION

The patients treated represent an advanced state of tumor growth: one-third required bilateral radical neck dissections; two-thirds were in Stage III and IV; and half the patients in Stage II had gross invasion of anterior cervical skin. Eleven of the 23 patients required tracheostomy prior to irradiation because of respiratory distress and 9 additional patients required tracheostomy during the period of radiation therapy. The survival rate to date is surprisingly good and while the group is too small to support significant conclusions it provides strong reason to continue the study.

Table VII

EFFECT OF IRRADIATION ON TUMOR HISTOLOGY AT OPERATION

Primary Lesions	23
No evidence of tumor	5
Marked tumor response	8
Moderate tumor response	9
No tumor response	1
Palpable Lymph Nodes Prior to Irradiation	12
No tumor in lymph nodes	8
Positive lymph nodes	4
No Palpable Lymph Nodes Prior to Irradiation	11
No tumor in lymph nodes	7
Positive lymph nodes	4

SUMMARY

A preliminary analysis of the results of integrated therapy of carcinoma of the larynx (18 patients) and hypopharynx (5 patients) is presented. There were no deaths from therapy and the morbidity was comparable to that of operation alone. Sixteen of 17 patients followed 1 year are surviving, as are 7 of 8 patients followed 2 years and all of 3 patients followed 3 years. These results are favorable enough to recommend continuation of the study.

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TREATMENT OF CERVICAL LYMPH NODE METASTASIS FROM PRIMARY LESIONS OF THE OROPHARYNX, SUPRAGLOTTIC LARYNX AND HYPOPHARYNX*

By ROBERT LINDBERG, M.D., *and* RICHARD H. JESSE, M.D.
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RADICAL neck dissection has been the most effective method of eradicating cancer in the cervical lymph nodes of patients with oral cavity cancer since Crile first introduced the procedure in 1905. Duffy,[2] in a 1938 review, concluded that radical neck dissection should not be employed for many patients with advanced metastasis which is usually associated with primary cancer of the oropharynx and hypopharynx.

Recently the rationale of radical neck dissection used alone for treatment of cervical lymph node metastasis has been challenged by those who believe that with the addition of radiation therapy a higher control of cancer in the neck can be achieved. Beahrs and Barber[1] report 25 per cent, and Strong *et al.*[6] 33 per cent recurrence in the neck of patients following radical neck dissection alone. These two series include many patients with oral cavity cancer in whom greater control of neck metastasis is expected than in those patients with the more virulent cancers of the oropharynx, hypopharynx and supraglottic larynx. No data are available regarding recurrence in the necks of patients with cancer of the oropharynx, hypopharynx or supraglottic larynx who have undergone radical neck dissection as part of their treatment.

The incidence of cervical metastasis in patients with squamous cell carcinoma of the upper respiratory and digestive tracts varies greatly depending upon the site of origin. We have found the incidence of cervical lymph node metastasis in patients on first admission to M. D. Anderson Hospital to be 87 per cent for nasopharynx, 76 per cent for base of tongue, 76 per cent for tonsillar fossa, and 72 per cent for those that originate on the palatine arch.[7] The high incidence of cervical metastasis associated with primary cancer in these sites is also likely to be in advanced state, as evidenced by multiple lymph nodes, bilateral lymph nodes, or large fixed lymph nodes. By contrast, cervical metastasis in patients with oral cavity cancer occurs much less frequently and is often in a relatively early stage, as indicated by small single lymph nodes.

At the M. D. Anderson Hospital a treatment regimen of combined megavoltage radiation therapy and surgery for cancer of the head and neck has been used since 1954. It is the purpose of this paper to examine (1) the effectiveness of radical neck dissection alone, and (2) the additive effectiveness of radiation therapy to radical neck dissection in the control of cancer in the neck.

MATERIAL

The records of 1,008 patients with cancer of the oropharynx, hypopharynx and supraglottic larynx observed from January 1954 through August 1962 were reviewed. Clinical staging of the cervical lymph nodes was determined on all patients at their initial observation, according to the

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From the Department of Radiotherapy and Section of Head and Neck Surgery, The University of Texas, M. D. Anderson Hospital and Tumor Institute at Houston, Houston, Texas.
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Table I

REGIONAL LYMPH NODE METASTASES

N_0	No clinical evidence of lymph node metastasis
N_1	A single ipsilateral clinically positive lymph node less than 3 cm. in diameter, not fixed
N_2	A single lymph node, ipsilateral, not fixed, more than 3 cm. in diameter, or multiple lymph nodes ipsilateral, not fixed, of any size
N_3	Bilateral or fixed unilateral or contralateral lymph nodes, clinically containing metastatic disease

method long employed in this hospital (Table 1). The records of 291 patients on whom a radical neck dissection was performed were selected for analysis.

The treatment was considered successful if the patient's neck was free of cancer at 3 years, since 90 per cent of the recurrences are manifest by 24 months. The treatment was also considered successful in the group of patients dead of any cause prior to 3 years if the neck was free of cancer at time of death. Treatment was considered a failure if the neck contained cancer even in those patients whose treatment for the primary lesion was also unsuccessful.

POLICY OF TREATMENT

OROPHARYNX CANCER

The oropharynx is divided into the palatine arch (soft palate, anterior tonsillar pillar, retromolar trigone) and the oropharynx proper (tonsillar fossa, pharyngeal walls and base of tongue). The treatment for primary oropharynx cancers of most patients, with selected exceptions, is by radiation therapy. The treatment programs for both the primary and cervical area have been previously reported in detail.[3,5]

Palatine arch. Patients with lesions on the palatine arch who are staged N_0 receive no irradiation or operation upon the neck. The upper ipsilateral neck of patients staged N_1 is irradiated and also receives subsequent radical neck dissection. A patient's neck, classified N_2 or N_3, will receive bilateral radical irradiation with subsequent unilateral or bilateral neck dissection.

Oropharynx proper. The treatment of the neck of patients with cancer of the oropharynx proper varies according to the site of the primary lesion. Patients with tonsillar fossa cancer, staged N_0, receive irradiation only to the upper ipsilateral neck, while those staged N_1, N_2, or N_3 receive radical irradiation to the entire neck. Radiation therapy usually controls the small multiple lymph nodes often associated with tonsillar fossa cancer and radical neck dissection is rarely necessary. A radical neck dissection is performed in those patients whose neck lymph nodes are greater than 4 cm. in diameter, are fixed, or do not regress after radiation therapy.

Patients with small cancers of the oropharyngeal walls are treated by radiation therapy, whereas those with large lesions are operated upon without prior irradiation. If the primary lesion is being irradiated, the ipsilateral jugular chain of lymph nodes is always included in the primary field, even if the neck is clinically negative. In the last 2 years the retropharyngeal lymph nodes have been included in the treatment field. If lymph nodes are present, the neck is radically irradiated and subsequent radical neck dissection is performed. If the patient's primary cancer is being treated surgically, a radical neck dissection is performed routinely on the ipsilateral side regardless of the lymph node classification.

Patients with cancer of the base of the tongue receive radical irradiation to the primary lesion and to the entire neck. Unilateral or bilateral neck dissection is done subsequently if the original lymph node was over 2 cm. in diameter.

SUPRAGLOTTIC LARYNX CANCER

Our usual treatment of patients with large or fixed lesions of the supraglottic larynx is wide-field laryngectomy. Neck dissection is not performed in a clinically

TABLE II

OROPHARYNX, SUPRAGLOTTIC LARYNX AND HYPOPHARYNX

(1954–August, 1962)

291 Patients

Failure to Control Cervical Disease

	N_0 and N_1	N_2 and N_3	Total
Radical Neck Dissection Alone	7/75 (9.3%)	23/71 (32.4%)	30/146 (20%)
Radical Neck Dissection and Radiation Therapy	4/39 (10.3%)	18/106 (17.0%)	22/145 (15.2%)

negative neck. Radical neck dissection unilaterally or bilaterally, as indicated, is performed on those patients with clinically positive lymph nodes. Postoperative radiation therapy is employed only if the surgeon suspects that there is cancer remaining in the neck. Those patients with a more exophytic lesion in a mobile larynx and clinically positive lymph nodes in the neck receive radical irradiation to both the primary lesion and the neck. Neck dissection is performed 4 to 6 weeks later. Laryngectomy is not done if the primary lesion is controlled.

HYPOPHARYNX CANCER

The treatment of patients with small (T_1) cancers of the hypopharynx is radiation therapy; the treatment field always covers the jugular chain of lymph nodes, and for the last 2 years has also included the retropharyngeal lymph node area. If metastasis is present in other than the jugular chain, radical irradiation of the entire neck is done, followed by radical neck dissection in 4 weeks. Most patients with primary cancers classified T_2, T_3, and T_4 receive laryngopharyngectomy and ipsilateral radical neck dissection regardless of the classification of the cervical lymph nodes. Usually the radical neck dissection is extended to include the parapharyngeal and retropharyngeal lymph nodes of Rouvier which are sometimes involved. Postoperative radiation therapy is given patients in whom there is any doubt about the adequacy of the resection.

For a 3 year period postoperative radiation therapy was given all patients with hypopharynx cancer to decrease mucosal recurrence. This practice was abandoned when the use of free skin grafts allowed the surgeons to remove more mucosa with immediate repair of the pharynx.

RESULTS

One hundred and forty-six of the 291 patients in the series had radical neck dissection as the only therapy to the neck. Thirty, or 20 per cent, of this group had neck recurrence. Of the 71 patients classified N_2 or N_3, there was a 32.4 per cent recurrence after neck dissection (Table II).

One hundred and forty-five patients had radiation therapy to the neck either before or after radical neck dissection. In 22 patients, or 15.2 per cent, the treatment was unsuccessful. Of 106 patients in this group classified N_2 or N_3, only 18, or 17.0 per cent, had recurrence in the neck.

Radiation therapy increased the effectiveness of the radical neck dissection in the entire series by 24 per cent. For those patients staged N_2 or N_3, however, the recurrence rate dropped by 47 per cent (32.4 per cent to 17.0 per cent).

Oropharynx. One hundred and forty-eight patients with oropharynx cancer had radical neck dissection; of whom 74 had radical neck dissection alone, 71 had irradiation of the neck with subsequent radical neck dissection, and 3 had radical neck dissection followed by radiation therapy. The number of patients in each "N" stage with the results of the treatment of the neck is shown in Table III. An improvement of almost 50 per cent was experienced by the group who received sequential radiation therapy and radical neck dissection. There was no difference in the two groups with cervical metastasis that was small and single (N_1). There was great improvement, however, in the patients

TABLE III

OROPHARYNX CANCER

(1954–August, 1962)
148 Patients
Failure to Control Cervical Disease

	N_0	N_1	N_2	N_3	Total
Radical Neck Dissection Alone—74 Patients	1/18 (5.5%)	3/21 (14%)	10/26 (38%)	5/9	19/74 (27%)
Sequential Radiation Therapy and Surgery—71 Patients	0/6	2/14 (14%)	5/27 (18.5%)	3/24 (12.5%)	10/71 (14.1%)

3 Additional Patients-Planned Surgery and Postoperative Radiation Therapy: $N_1 = 1$ case, $N_2 = 1$ case, $N_3 = 1$ case (uncontrolled cervical disease).

with advanced neck metastasis (N_2 and N_3).

Supraglottic larynx. The small number of patients in the supraglottic group makes comparison of statistics difficult. A slightly better control of lymph node metastasis is apparent in those patients who had postoperative irradiation as compared to those having radical neck dissection alone (Table IV).

There was slightly less effective control of the cancer in the neck in the group treated by sequential radiation and surgery, the latter for persistent or recurrent disease. Radiation therapy was chosen in preference to surgery for these patients in an effort to conserve larynx function. The choice of this therapy in these patients resulted in a slightly higher recurrence of cancer, both in the primary area and in the neck.

Hypopharynx. Thirty-eight of 83 patients with hypopharynx cancer underwent radical neck dissection alone (Table V). Eighteen per cent of these patients had recurrent cancer in the neck, mostly in those classified N_2 or N_3. In the patients irradiated after radical neck dissection, control of the disease in the neck in the N_2 and N_3 groups was much better. The number of patients who had radical neck dissection after irradiation is too small to be of significance.

DISCUSSION

The policies of treatment as outlined

TABLE IV

SUPRAGLOTTIC CANCER

(1954–August, 1962)
60 Patients
Failure to Control Cervical Disease

	N_0	N_1	N_2	N_3	Total
Radical Neck Dissection Alone—34 Patients	0/3	2/16	0/10	2/5	4/34 (11.7%)
Sequential Radiation Therapy and Surgery—13 Patients	—	2/5	1/5	0/3	3/13 (23%)
Planned Surgery and Radiation Therapy—13 Patients	0/1	0/3	0/7	1/2	1/13 (7.7%)

Table V

HYPOPHARYNX CANCER
(1954–August, 1962)
83 Patients
Failure to Control Cervical Disease

	N_0	N_1	N_2	N_3	Total
Radical Neck Dissection Alone—38 Patients	0/7	1/10 (10%)	3/13 (23%)	3/8	7/38 (18%)
Sequential Radiation Therapy and Surgery—11 Patients	0/3	0/2	0/2	2/4	2/11 (18%)
Planned Surgery and Radiation Therapy—34 Patients	0/2	0/2	1/14 (7%)	4/16 (25%)	5/34 (15%)

above are only guides and are not inflexible. The surgeon and radiotherapist together arrive at a consensus regarding a patient's treatment after evaluating his primary cancer, the status of the cervical lymph nodes, his general condition, his social-economic factors, and his habits—particularly smoking and drinking. Therefore, 2 patients presenting with similar cancers may not have similar treatment, since their ability to adjust and to withstand the therapy may be different. We try to cure the greatest number of patients without causing them undue disability. We believe that combinations of radiation therapy and surgery cause fewer complications and less disability than either modality extended beyond the usual therapeutic level.

Our experience indicates that most small single lymph nodes less than 3 cm. in diameter can often be sterilized by radiation therapy or removed surgically with an equal chance of success. When the lymph node is greater than 3 cm. in diameter, it frequently breaks through the capsule and spreads into the soft tissue of the neck. Under these conditions, recurrence in the neck after radical neck dissection or ordinary doses of radiation therapy is likely to occur. Therefore, in these patients we either increase the radiation dose to the neck to a high level (8,000 rads or above) or use combinations of radiation therapy and surgery. In patients whose neck is classified as N_2 or N_3 we have chosen radical irradiation, either prior or subsequent to radical neck dissection. The preoperative irradiation has been a minimum of 5,000 rads given dose, in 5 weeks, delivered to the ipsilateral side of the neck. Patients in whom the primary lesion is to be treated by radiation therapy, the field covering the lesion and the ipsilateral neck receives a minimum of 6,000 rads given dose in 6 weeks, with some patients receiving an additional 1,000 rads boost through a greatly reduced portal. The minimum radical neck dissection employed in these irradiated patients is the standard Crile procedure. However, the dissection is often extended into the retropharyngeal lymph node area, particularly in those patients with lesions of the oropharyngeal and hypopharyngeal walls. The surgical mortality of radical neck dissection alone or in combination with resection of the oropharyngeal, supraglottic or hypopharygeal primary lesion in the nonirradiated patient is 4.8 per cent, while this increases to 5.3 per cent for the prior irradiated patients. Most of the mortality is due to exposure and subsequent rupture of the carotid artery through an unhealed wound. In recent years the incision for radical neck dissection has been altered from a trifurcate incision to a bifurcate incision in irradiated patients. As a result, exposure of the carotid artery is now virtually non-

existent. It is interesting to speculate whether the preoperative dose of 2,000 rads given in 5 days, immediately followed by surgery as advocated by Henschke *et al.*,[4] would obtain the same result as our radical pre- or postoperative irradiation with less mortality and morbidity to the patient. In our present series with a 3 year follow-up, we find that only 15.2 per cent of the patients in whom the primary cancer was of high virulence who were treated with irradiation and radical neck dissection had recurrence. Strong *et al.*[6] report a recurrence rate of 22.5 per cent in the neck after the lower irradiation dose and radical neck dissection in a series predominantly composed of patients with oral cavity primary cancers and hence of somewhat less virulence than our series. We feel that the higher dose of irradiation offers the best prognosis for most patients since it significantly lowers the rate of recurrence.

SUMMARY

The records of 291 patients with cancer of the oropharynx, supraglottic larynx and hypopharynx in whom radical neck dissection was performed were reviewed. There was failure to control the cancer in the neck in 30 of 146 patients (20 per cent) who had radical neck dissection alone. In 145 patients receiving radiation therapy either prior or subsequent to the neck dissection, there was a failure to control the cancer in the neck in 22, or 15.2 per cent. The addition of radiation therapy to radical neck dissection does not improve the results in those patients with single ipsilateral lymph nodes less than 3 cm. in diameter (N_1); however, almost 50 per cent improvement (32.4 per cent recurrence *versus* 17.0 per cent recurrence) is obtained by adding radiation therapy to radical neck dissection in patients with multiple, fixed, or bilateral cervical metastasis (N_2 and N_3).

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THE ROLE OF ROENTGENOGRAPHIC STUDIES IN THE EVALUATION AND STAGING OF MALIGNANCIES OF THE LARYNX AND PHARYNX*

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THIS is a report on 105 consecutive cases of cancer of the larynx and/or pharynx examined roentgenographically at the Medical College of Virginia from April, 1963, to March, 1966.

The proper diagnosis of malignancies of the larynx or pharynx, the classification, subsequent treatment, and follow up, demand evaluation of the exact extent of involvement of tissues by the primary lesion at the initial study. Furthermore, when radiation therapy is employed in this region, the proximity of vital structures requires that the area of treatment be as small as possible, yet fully encompass the lesion.

The currently available clinical methods of evaluation of cancer of the larynx and pharynx as described by the American Joint Committee on Cancer Staging and End Results Reporting,[1,2] are the following: (1) palpation; (2) endoscopic study: (a) indirect (mirror), (b) direct (laryngoscopic, bronchoscopic, esophagoscopic); and (3) roentgenographic examination.

Utilization of all of these methods allows an accurate determination of the extent of primary lesions of the larynx and pharynx.

NONROENTGENOGRAPHIC METHODS

Of the clinical methods available, the majority of information previously formulated in the investigation of the extent of primary lesions of the larynx and pharynx has been on the basis of the nonroentgenographic modalities of palpation and endoscopic examination—methods which may not yield the desired result. Considerably less emphasis has been placed on the use of diagnostic roentgenographic examination as an additional method of determining the extent of tumor involvement.

Palpation. Digital palpation of primary lesions especially those of the base of the tongue, epiglottis, and valleculae, is helpful in determining the gross characteristics of that portion of these tumors which can be reached, but not beyond.

Endoscopic Study. Endoscopic study by indirect (mirror), and direct (laryngoscopic, bronchoscopic, and esophagoscopic) methods allows visual inspection of the lesions and also permits investigation of the disturbances in intrinsic movements. However, in certain instances there are definite deficiencies in this method of examination. Pastore *et al.*[8] noted that lesions involving the region of the base of the tongue, laryngeal surface of the epiglottis, pyriform sinuses, postcricoid and subglottic surfaces, because of their anatomic location, may be relatively inaccessible to complete evaluation by endoscopic instruments. In addition, exophytic tumors may allow only inspection of their upper surfaces precluding evaluation of any distal lesion or the inferior surface of the primary tumor. Furthermore, limitation of movement of the jaw and tongue, when present, limits visual inspection and introduction and manipulation of the evaluating instruments.

ROENTGENOGRAPHIC METHODS

The currently employed roentgenographic methods are those of plain film examination, laminography, barium swallow study, and examination of the positive contrast coated larynx and pharynx (laryngopharyngography).

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Plain Film Examination and Laminography. Plain film examination, as emphasized by Coutard in 1922,[3] and laminography of the neck, introduced by Leborgne[6,7] in 1940, are highly informative as regards the integrity of the calcified cartilages of the neck. The extent of soft tissue information obtainable by these methods, however, is limited in that an air and soft tissue interface is required for definition. These studies also have limited usefulness in rendering information concerning the functional integrity of the larynx and pharynx.

Barium Swallow Study. Observation and recording of the dynamic act of swallowing yield both functional and structural information concerning the larynx, pharynx, and the cervical esophagus. The recent introduction of cineroentgenographic and television tape recording has greatly increased the effectiveness of this method, allowing more careful study of rapid movement.

Laryngopharyngography. The excellent depiction of the anatomic structures of the pharynx and larynx with positive contrast coating was noted as early as 1918 by Jackson[5] and later by Fariñas, in 1942.[4] A diagnostic roentgenographic study using this method of investigation specifically was described in 1948 according to Di Gugliemo. This modality was introduced in the United States in 1957 by Powers *et al.*[9,10]

Of the roentgenographic methods available to examine the larynx and pharynx, the positive contrast coated examination is the most informative, and when combined with plain film examination and barium swallow study constitutes a complex yielding very valuable information of the structural and functional alterations which may be encountered in malignancies of the larynx and pharynx.

Detailed descriptions of the technique of performance of laryngopharyngography have been given elsewhere.[8] A brief description of the technique emphasizing certain aspects of this study is as follows: Thorough explanation of the maneuvers to be performed is generally necessary to assure understanding and cooperation of the patient. Very apprehensive patients may need mild sedation, but usually none is required. Atropine sulfate must be used in fairly large quantity. An amount sufficient to give thorough drying of the mucous membranes is a prime prerequisite to a satisfactory study, allowing more complete contact with the dried mucosa of anesthetic and later of liquid positive contrast agent. Our routine calls for an initial dose of 1.2 mg. of atropine sulfate given intramuscularly 45 minutes before the procedure. If after 45 minutes the drying effect is still not adequate, an additional 0.8 mg. of atropine sulfate is given intravenously. Following topical anesthesia of the oro-laryngopharynx, larynx, and upper trachea, liquid positive contrast material (dionosil oily)* is dripped into the posterior oro-pharynx, pyriform sinuses, and larynx by means of a flexible curved metal cannula attached to a syringe with the patient sitting upright. In spite of adequate anesthesia, at this point the patient is definitely aware that a foreign material is present in the pharynx and larynx, and must be instructed not to cough or swallow.

When the coating of surfaces by contrast agent is satisfactory, spot roentgenograms and cineroentgenographic recording are made in frontal, lateral, and oblique projections during quiet breathing (with the cords abducted), phonation (with the true cords adducted), Valsalva maneuver (with the glottis closed), and modified Valsalva maneuver (blowing against pursed lips to balloon the pharynx). A cineroentgenographic recording of rotation of the neck through 180° allows a tangential view of all aspects of the coated surfaces.

The procedure is contraindicated when the disease has compromised the airway. In such circumstances mild tissue reaction to the agents used may be sufficient to

* Dionosil Oily is the registered trademark for propyliodone oil suspension manufactured by Glaxo Laboratories Ltd., Greenford, England.

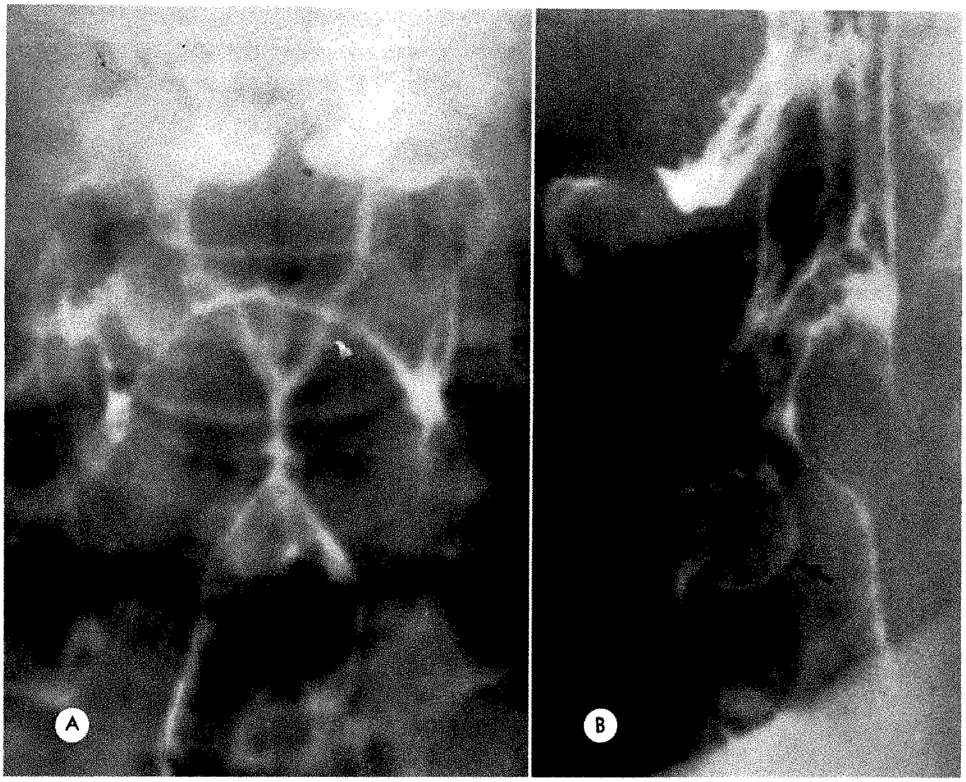

FIG. 1. Case I. (*A*) Frontal and (*B*) lateral roentgenograms of positive contrast study. Rounded exophytic mass of the right true vocal cord projecting inferiorly (single arrows). Tumor crossing the midline anteriorly obliterates the anterior portion of the immediate subglottic area (open arrow in *B*).

precipitate severe respiratory distress. These patients should have tracheostomy prior to the procedure.

REPORT OF CASES

CASE I. A 45 year old male was seen in September, 1964, with a history of intermittent hoarseness and voice fatigue of 6 months' duration, progressing throughout the day with voice use. He denied any weight loss, loss of appetite or difficulty in swallowing. In the past, he had smoked one plus package of cigarettes per day for 15 years. Ingestion of alcoholic beverage had been averaging four-fifths quart per week for 20 years.

Pertinent Physical Examination. Except for a hoarse, raspy voice, there was a normal examination. There were no palpable lymph nodes in the neck.

Indirect Laryngoscopy. This was essentially negative with the right true cord demonstrating an irregular border; the upper surfaces and ventricles of Morgagni were normal. A biopsy from the free border of the right cord showed squamous cell epithelioma.

Laryngopharyngography. September, 1964. (Fig. 1, *A* and *B*). There was tumor infiltrating the right true cord with some irregularity of the free border and exophytic, somewhat pedunculated tumor extending into the subglottic space but attached to the cord. There was diminished right cord motility; the ventricles of Morgagni were preserved bilaterally. Stage I; $T_1 N_0 M_0$.

Treatment. The patient was referred for radiation therapy and received 7,000 r mid-larynx tumor dose through lateral opposing ports in 35 days, terminating in November, 1964.

Follow up. To date, the patient is alive and well without evidence of recurrent disease.

CASE II. This 67 year old female was seen in August, 1964, with a history of progressive blindness due to cataracts over the past 16 years; she also noted inability to eat solid foods 2–3 months ago and has had excessive oropharyngeal secretions and drooling. There was a

30 pound weight loss during the past 3–4 months due to dysphagia. There had been no bleeding from the throat area but an intermittent swelling of the neck had been noted for the past 2 months. The patient denied smoking or drinking alcoholic beverages.

Pertinent Physical Examination. The patient appeared older than the stated age. There was a rather firm, fixed 3×4 cm. mass in the right submandibular area. The neck was supple with palpable lymph nodes in the anterior cervical chain.

Pathology. Although no records of an endoscopic examination could be found, a biopsy report of tissue from the left pyriform sinus stated, "Poorly differentiated squamous cell epithelioma."

Laryngopharyngography. (Fig. 2). A bulky tumor with ulceration extended from the mid left aryepiglottic fold to the postericoid area. There was fixation of the left true cord, and no movement of the left arytenoid was noted. The left pyriform sinus was partially obliterated by the tumor involving its anterior aspect. Stage IV; T_3 N_2 M_0.

Treatment. Gastrostomy and tracheostomy. Radiation therapy: 6,000 rads were delivered through lateral opposing ports to the neck, lymph nodes and tumor site in 33 treatment days, being completed in October, 1964.

Follow up. The patient was lost to follow up for several months, but was seen in November, 1965, 13 months after radiation therapy, when progression of the tumor was noted. Since that time, the patient has again been lost to follow up.

Fig. 2. Case II. Lateral roentgenogram of positive contrast study. Lobulated tumor mass extends from mid-aryepiglottic fold above to postcricoid area below (arrows).

Case III. This 44 year old female was first seen in July, 1965, with a complaint of episodic sore throats for the past 7 months, and difficulty in swallowing of 6 weeks' duration. She had also had intermittently a mild earache radiating from the throat on the left.

Pertinent Physical Examination. There was a single palpable mobile lymph node in the anterior cervical chain at the level of the thyroid cartilage on the left. Otherwise, nothing remarkable was found on examination.

Laryngoscopy. July 18, 1965. Direct and indirect: There was noted an exophytic tumor of the epiglottis and left aryepiglottic fold extending into the valleculae at the base of the tongue and into the pharyngeal lumen precluding examination of distal points.

Laryngopharyngography. July 21, 1965. (Fig. 3, *A* and *B*). There was an exophytic tumor replacing the epiglottis extending proximally along the aryepiglottic folds, more so on the left. The valleculae were filled with tumor mass. The pharyngeal surface of the epiglottis was covered by tumor. Distally the pyriform sinuses were mobile and free. The laryngeal surface of the epiglottis was free of tumor. The true and false cords were edematous but moved well. The postcricoid area was normal. Stage III; T_3 N_1 M_0.

Treatment. The patient had 2,400 rads preoperative irradiation to the pharynx through lateral ports and on August 13, 1965 underwent a supraglottic pharyngectomy, partial glossectomy and left radical neck dissection.

Follow up. The patient was last seen in March, 1966, and was doing well without evidence of tumor and gaining weight.

Case IV. This 57 year old male was seen in March, 1963, when he had noted pain on coughing and swallowing for the past 4–6 months, associated with a persisting nasopharyngitis. He

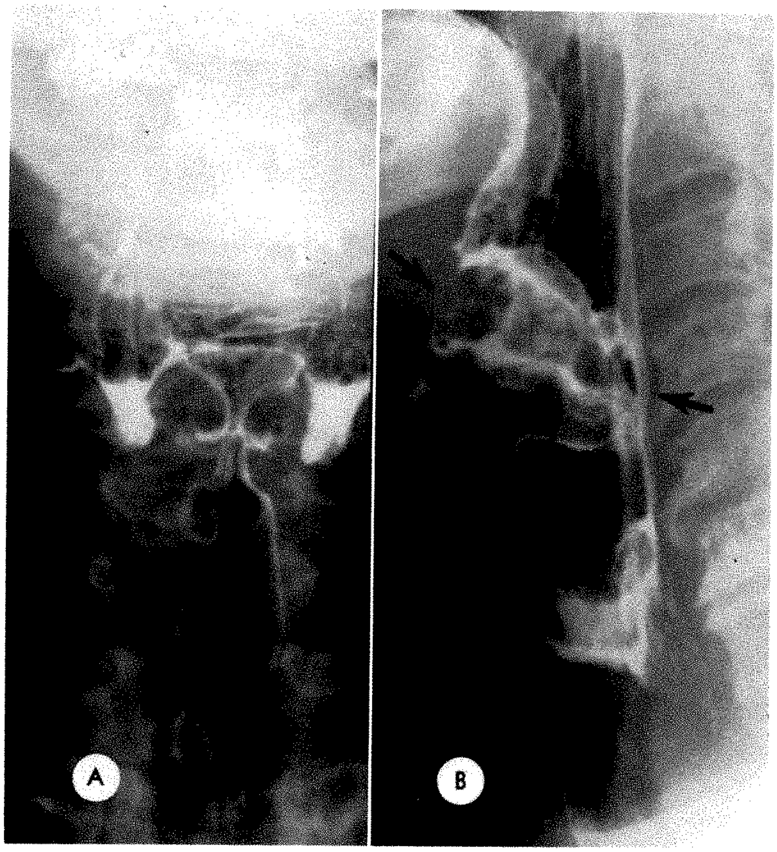

FIG. 3. Case III. (*A*) Frontal and (*B*) lateral roentgenograms of positive contrast study. Exophytic tumor replacing epiglottis extends to fill the valleculae and along the pharyngeal surface of the epiglottis and proximal aryepiglottic folds (arrows).

had had hemoptysis intermittently for the past 10 days. No hoarseness or weight loss was noted. In the past, he had smoked one pack of cigarettes per day for 30 years. He had drunk socially 2–3 highballs on the weekend for 20–30 years.

Pertinent Physical Examination. Lymphoid hyperplasia of the posterior pharynx with post nasal discharge was noted. The patient had fetor oris. The neck was supple with no palpable masses or lymph nodes.

Laryngoscopy. Direct and indirect: There was a friable, bulky exophytic tumor extending into the right pyriform sinus from the aryepiglottic fold on the right.

Laryngopharyngography. April, 1963. (Fig. 4*A*). There was a bulky exophytic tumor involving both walls of the right pyriform sinus. The postcricoid area was free of tumor. The true and false cords were normal and moved well. Stage II; T_2 N_0 M_0.

Treatment. The patient had radiation therapy to the neck area encompassing the tumor through lateral ports; 6,600 rads was given to mid-plane pharynx in 33 treatment days, terminating in June, 1963.

Post Therapy Laryngopharyngography. February, 1966. (Fig. 4*B*). Essentially normal study with the pyriform sinus ballooning well on pressure maneuver (modified Valsalva maneuver).

Follow up. The patient has shown no recurrence of disease to date.

RESULTS

Full utilization of the roentgenographic modalities of examination in 105 consecutive cases of cancer of the larynx and/or pharynx at the Medical College of Virginia from April, 1963 to March, 1966, has allowed more complete evaluation of the

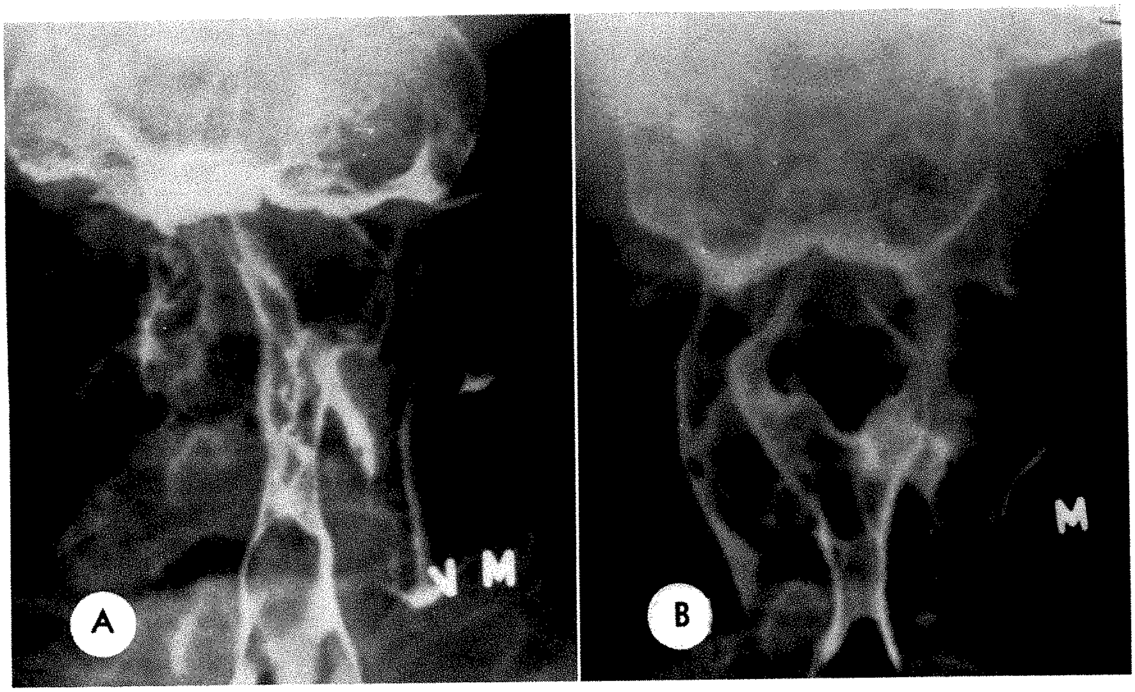

Fig. 4. Case iv. (*A*) *April, 1963:* Positive contrast study done prior to roentgen-ray therapy. Frontal projection of ballooned pharynx in modified Valsalva maneuver (blowing against puffed cheeks). Left pyriform sinus distends normally. Right pyriform sinus not distensible and replaced by extensively ulcerated mass. (*B*) *February, 1966:* Positive contrast study in frontal projection of modified Valsalva maneuver done 2 years 8 months after completion of roentgen-ray therapy. No evidence of tumor recurrence. The right pyriform sinus is reformed and covered with smooth mucosa and has a moderate degree of distensibility.

lesions in locations relatively inaccessible to other forms of study (Fig. 1, *A* and *B*; and 2).

The inferior extent of bulky lesions and the structures hidden from endoscopic view by the volume of the lesion have been readily demonstrated (Fig. 3, *A* and *B*).

Instances of limitation of jaw or tongue mobility have not prevented adequate roentgenographic examination.

Complete roentgenographic examination in all these cases has provided a visual guide to therapy, and has established a firm document for follow up study in evaluation of the results of therapy (Fig. 4, *A* and *B*) and in evaluation of the possibility of recurrent disease.

SUMMARY

Proper management of patients with cancer of the larynx or pharynx requires complete information regarding the extent of the disease.

The clinical methods of evaluation of the primary lesions as recommended by the Joint Committee of Cancer Staging and End Result Reporting are reviewed.

Emphasis is placed on the full utilization of the roentgenographic modalities of clinical evaluation, including study by positive contrast coating of the larynx and pharynx (laryngopharyngography).

The method of laryngopharyngography is briefly described.

The advantages of full roentgenographic study with illustrations of selected cases from the records of the Medical College of Virginia are presented.

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HEAD IMMOBILIZATION UNIT IN AID OF HEAD AND NECK TUMOR TREATMENT*

By YUNG H. SON, M.D.†
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REPRODUCTION of the patient's position is essential, particularly in treating head and neck tumors. In 1963, Perez-Tamayo and Seibert[1] introduced a unit suitable for this purpose.

The author presents an improved model easily attachable to a treatment table currently available (Fig. 1).

While the patient's head rests comfortably on a cushioned head-rest each of two ear-pieces is introduced into the external auditory meatus. Once the patient's head is maintained in a desired position, a nose-piece is brought to rest on the nasion. This nose-piece may be used as a chin-holder. Two toggle clamps on a swivel extension arm will hold a port film cassette. After a port film has been exposed, the arm may be swiveled out of the beam pathway (Fig. 2).

This unit has proved expeditious and useful in accurate reproduction of positioning the patient's head.

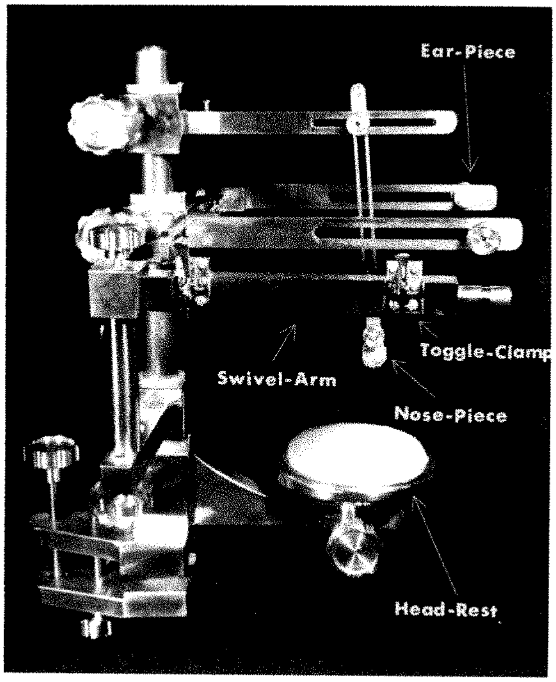

Fig. 1.

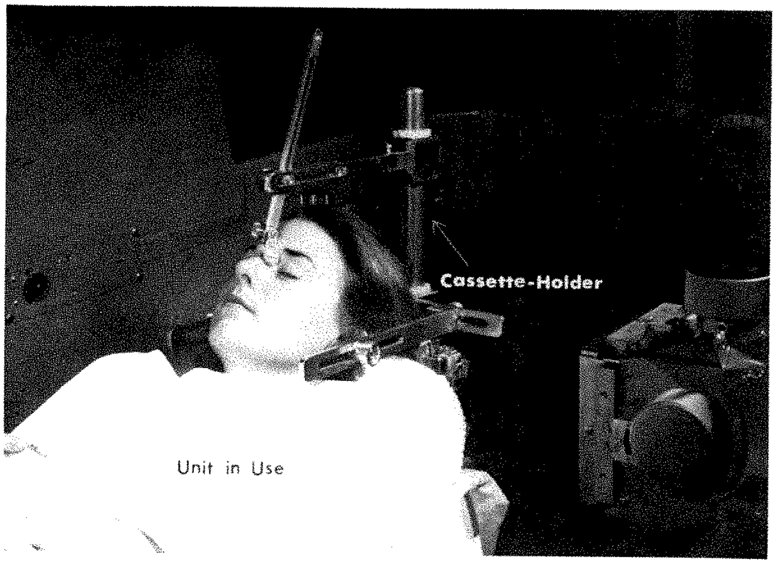

Fig. 2.

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SUMMARY

An improved head-immobilizing unit is presented.

Its versatility, easy applicability, comfort and built-in cassette-holder are definite advantages over the existing unit.

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I wish to thank Mr. E. F. Spenceley of Research Laboratory for the Engineering Services at the University of Virginia for building the unit to the specifications.

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Vol. 102, No. 1

THE SURGICAL TREATMENT OF CANCER OF THE CERVIX: STAGE I AND II*

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THE answer to the question, which is the preferred treatment for cancer of the cervix, surgery or radiation therapy or a combination of both, cannot be given simply by comparing statistics from one institution pursuing a radiation therapy program with another one pursuing a surgical program. Time should no longer be wasted in belaboring such comparisons.

The purpose of this report is to review the experiences obtained in as purely surgical program as is feasible to carry out in a clinical center today. The series presented is the largest modern surgical series so far recorded and this was possible because at the outset of the program the policy of regarding all cases as purely surgical problems was formally established. Among the 1,087 patients not previously treated 800 patients were operated upon "to cure." Eight hundred and seventy-one received laparotomy, 9 received no treatment, 5 consultation only, and 53 refused operation; 149 received radiation therapy only for various reasons. Half of these were in Stage I and II and half were in Stage III and IV. These patients would have been operated upon except for a variety of extraneous reasons.

The question of classification is clarified in this series because the cases are recorded according to the Surgical Pathological Classification which is based upon the study of the excised specimens and pelvic lymph nodes. While in all cases, the pelvic lymph nodes were not excised, they were removed in most of them, and when not removed, a gross evaluation of the presence or absence of metastases was possible at laparotomy (with frozen sections, as called for) or by direct palpation of the pelvic walls if a radical vaginal hysterectomy or classical Wertheim operation was done. Where only pelvic examination is carried out prior to institution of radiation therapy, the classification is subjective. Likewise the newer T+ or −, N+ or − system recently mentioned in the literature can be followed only if there is a surgical specimen. In cases treated by radiation therapy there are no surgical specimens, therefore classification is purely subjective.

RESULTS

In conformity with the subject of the Panel Symposium, results in patients classified as Stage I and Stage II only are reported. It is the custom on the Service at Memorial Hospital first to classify all patients upon pelvic examination by following the rules listed in the Annual Report.[1] After the operation and return of the surgical pathological report, the case is classified according to the Surgical Pathological Classification.[3] In Table I, 591 patients staged as I or II are classified according to the surgical and pathological scheme. It is immediately noted how inaccurate pelvic examination is in permitting a true evaluation of the extent of cervix cancer. Among the 279 patients called Stage I only in 179 (64 per cent) did gross and microscopic study of the specimens reveal that cancer was indeed limited to the cervix. Also, among 312 patients called Stage II on clinical examination only 220 (68 per cent) were found to be actually limited to the cervix and immediate environs (Classes A, B, C, CN).

An interesting side-light afforded by the

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Part of Panel Symposium: Management of Stage I and II Carcinoma of the Uterine Cervix. Chairman, Gilbert H. Fletcher, M.D., Houston, Texas.
This study was facilitated by Grants from the James S. and Marvelle Adams Foundation, Greenwich, Connecticut; the Martin H. Crego Memorial Fund, donated by Jean Crego, New Canaan, Connecticut; and the Anne Wagner Foundation, Amarillo, Texas.

TABLE I

CORRELATION OF FIVE YEAR RESULTS

Surgical Program for Cancer of Cervix Classified According to International Clinical and Surgical Pathological Schemes

Surgical Pathological Classification	Clinically Called Stage I	Clinically Called Stage II	Totals
A Cervix only	151/179	37/51	188/230 (82%)
B Extension to fornices	39/49	70/114	109/163 (66%)
C Extension to parametria	4/7	19/39	23/46 (50%)
CN Same with positive parametrial lymph nodes	2/5	5/16	7/21 (33%)
D Positive lymph nodes at periphery of pelvis	14/24	13/27	27/51 (53%)
DC Same with positive parametria	5/11	9/35	14/46 (30%)
E Bladder, rectal, ureteral involvement	0/1	6/17	6/18 (33%)
EN Same with positive lymph nodes	0/1	2/5	2/6 (33%)
FN Pelvic wall or floor involvement with positive lymph nodes	1/2	0/8	1/10 (10%)
Total	216/279 (77.4%)	161/312 (51.6%)	377/591 (63.8%)

above method of classification on the host tumor relationship in that among 179 "true" Stage I cases 151 survived 5 years (84 per cent), whereas among 51 cases clinically staged as II because of clinical impression of "parametrial infiltration" but whose specimens still showed the cancer limited to the cervix (Class A), the 5 year survival was 37 (57 per cent). A possible explanation for this is that the more "virulent" or "aggressive" neoplasms from their initial inception stimulate a more violent host reaction, as evidenced by inflammatory thickening in the parametria.

As previously pointed out, the surgeon has 10 operations from which to choose in attacking cancer of the cervix.[2] The choice depends upon his own estimations of patient-risk and size of the lesion. Six hundred and twenty-eight cases staged as I and II are summarized in Table II. These include 37 patients not included in Table I because having received preoperative radiation therapy the specimens were reported as negative for cancer (they all had positive biopsies prior to radiation therapy). No patient had pelvic lymph node excision only, the tenth type of operation, in this series. The results achieved with the conservative operations, *i.e.*, excision of cancerous stump, radical vaginal hysterectomy (Schauta), classical Wertheim operation (not a radical operation by modern standards) and total hysterectomy, reveal that among 94 patients there were 61 five year survivors (65 per cent).

Among 32 patients who received an exenterative procedure there were 14 (44 per cent) five year survivors. This result, expressed in terms of type of operation contrasts with the five year survivors of 9 among 34 (36 per cent) expressed in terms of extent of disease (Classes E, EN, FN), indicating that in some instances exenterations were performed when they possibly need not have been and that in other instances they were not performed when they perhaps should have been.

LYMPHADENECTOMY

One of the advantages of the surgical treatment of cancer of the cervix is the possibility of pelvic lymph node and fatty fibrous tissue excisions which remove metastases when they are present and thus afford a chance for cure if cancer has not spread beyond. Among the 591 cases staged I and II there were 180 instances of cancer spread into the parametria, para-

Table II

5 YEAR SURVIVORS, STAGE I AND II (COMBINED)

Types of Operation

Operation	5 Yr. Survivors
Total Hysterectomy	16/17 (95%)
Classical Wertheim Operation (no positive lymph nodes)	17/35 (48.5%)
Radical Vaginal Hysterectomy (Schauta)	26/40 (65%)
Radical Hysterectomy + Lymph Node Dissection	296/444 (66.7%)
Excision of Cervical Stump + Lymph Node Dissection	38/58 (65.5%)
Excision of Stump Only	2/2
Posterior Pelvic Exenteration	2/3 } 14/32 (44%)
Anterior Pelvic Exenteration	10/26 } 14/32 (44%)
Total Pelvic Exenteration	2/3 } 14/32 (44%)
Total	409/628* = 65%

* Includes 37 cases with negative specimen after preoperative radiation therapy.

metrial lymph nodes, lymph nodes at the periphery of the pelvis and into bladder or rectum with pelvic lymph node metastases (Classes C, CN, D, DC, EN, FN) with 74 five year survivors (41 per cent). In patients who receive radiation therapy alone, it is impossible to evaluate directly the effect upon lymph node metastases. The achievement of 41 per cent five year salvage, where in this series positive pelvic lymph nodes were confirmed by histologic study and including 16 cases of adjacent organ invasion as well, testifies to the value of lymphadenectomy.

The statement has been made that lymphadenectomy is futile if there are lymph node metastases present after "full irradiation." What "full irradiation" means cannot be adequately defined but in the Memorial Hospital surgical series for treatment of *recurrent* cancer of the cervix following radiation therapy alone, conservative surgery and radiation therapy, and surgery alone (13 cases), there were 182 instances of pelvic lymph node metastases with 19 five year survivors (10 per cent). This certainly is far from satisfying, but even here the situation is not hopeless and certainly does not warrant the view that lymphadenectomy adds nothing if there are positive pelvic lymph nodes after radiation therapy failure.

THE COMBINATION OF SURGERY AND RADIATION THERAPY

Because of the firm establishment of radiation therapy for cancer of the cervix, the re-emergence of surgery in the field has been slow and limited. Considerable experience has been recorded in the combined use of surgery and radiation therapy, especially for patients in Stage I and II. As yet there is no unequivocable evidence that such combinations have definite advantages. Indeed there may be disadvantages. Certainly the clinical results do not indicate that the patients receive "the best of surgery plus the best of radiation therapy."

In the management of the 800 patients referred to here, it was not always possible to exclude preoperative or postoperative radiation therapy because: (1) patients would be admitted who had had radiation therapy "to cure" within 6 months elsewhere. These were empirically classified as having had "preoperative" radiation therapy, and were then operated upon according to the usual procedure; (2) some staff members felt that in the operation they did or supervised in which pelvic lymph node metastases were excised, the patients would benefit by postoperative radiation therapy. This was an individual action and

TABLE III

5 YEAR RESULTS OF SURGICAL TREATMENT OF CANCER OF CERVIX RELATED TO PELVIC LYMPH NODE METASTASES AND ASSOCIATED RADIATION THERAPY

	Surgery Only		Surgery+Associated Radiation Therapy* Some Preoperative Radiation Therapy Some Postoperative Radiation Therapy Some Pre- and Postoperative Radiation Therapy	
	Negative Lymph Nodes	Positive Lymph Nodes	Negative Lymph Nodes	Positive Lymph Nodes
Stage I Stage II	170/204 (83%) 105/177 (60%)	7/18 (39%) 12/43 (28%)	25/32 (78%) 27/44 (61%)	14/25 (56%) 17/48 (33%)
Total	275/381 (74.5%)	19/61 (31%)	52/76 (68.4%)	31/73 (42.4%)
All cases 294/442 = (66.2%)			83/149 = (55.7%) Including 37 cases sterilized by preoperative radiation therapy, of whom 32 survived 5 years: 115/186 = 61.8%	

* All cases had cancer in excised specimens.

not in accord with "policy." The result, however, was the development of two series, one large (444 cases) and one less extensive (186 cases) in which surgery alone, and surgery in combination with radiation therapy were used, all operations being done in the same institution. The results are summarized in Table III. In this study no benefits could be demonstrated by combination of radiation therapy with surgery if all cases are included. However, in a small selected group, *i.e.*, those called Stage I with positive lymph nodes, there is indication that postoperative radiation therapy may have afforded an increased 5 year salvage, but this entire series comprises only 53 patients.

DISCUSSION

A series of 628 patients clinically staged as I or II were treated surgically and this study, within the parameters described, would seem to qualify as a yardstick for what modern surgical treatment under usual clinical conditions for cancer of the cervix can accomplish. The factor of complementary radiation therapy, unavoidably for reasons given, also was employed in 186 cases—30 per cent of the series.

The results here recorded cannot be compared with the results achieved elsewhere by a purely radiation therapy program. The reasons are:

(1) The factor of selection of patients is a very real one and is not uniform from one center to another.

(2) The inclusion of carcinoma *in situ* is widespread and cannot be ruled out.

(3) Clinical examination with staging is highly subjective and where comparisons are made between clinical staging and pathological verification of the extent of the cancer, a 30 per cent error in the latter is documented (in this series), etc.

The conception of radical surgery for cancer of the cervix had been relegated to obsolescence over a period of about 30 years among gynecologists, who first see these patients, so that the idea of operating upon them has become regarded as a "heresy."

Actually there is no justification for this until it has become unequivocally proved that radiation therapy is superior in every way and in each patient to surgery. The mortality for surgery in Stage I and II has

been reduced to 1.6 per cent, practically the same as for radiation therapy.

In the author's opinion there is still no basic reason why radical excision of a cervical cancer together with pelvic lymph nodes should not be the preferred treatment for any given case of cancer of the cervix Stage I or II. Mitigating circumstances could include advanced age, medical complications, marked obesity, etc., where radiation therapy may be indicated. Also, in women still in their twenties or thirties, the preservation of ovarian function is highly desirable and by appropriate radical operations the cancer and adjacent lymph node group can be widely and adequately excised preserving both ovaries. The assurance to younger patients that preservation of their functioning ovaries is possible constitutes an important factor in maintenance of morale, to say nothing of the preservation of the flexibility of the vagina.

At present, it is to be admitted, that the training facilities for the radical surgical management of cancer of the cervix are limited indeed, and therefore the number of patients to be treated in this manner is restricted. However, interest in the surgical management is gradually increasing throughout the world, in particular for selected good risk subjects with lesions in Stage I and II, and in some form of combination with radiation therapy.

SUMMARY

1. The results of a surgical program in the treatment of cancer of the cervix in Stage I and II are reviewed. Two thirds were treated by surgery alone; one third were operated upon according to the same principles but, unavoidably, received associated radiation therapy. The over-all results showed no improvement in the combined series over the purely surgical series; the surgical procedures in the combined series were carried out in an identical manner with the purely surgical series.

2. The inaccuracies of clinical staging are documented by comparison with the Surgical Pathological Classification of the same series of patients in which it was shown that about one third of the cases showed more extensive disease than suspected upon clinical examination alone.

3. Evidence is presented to indicate that pelvic lymphadenectomy is of significance in augmenting the five year "cure" rate of cancer of the cervix.

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SEQUENTIAL RADIATION THERAPY AND SURGERY FOR STAGE I AND STAGE II CANCER OF THE CERVIX*

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THE possibility of combining irradiation and radical pelvic surgery to the advantage of the patient with Stage I or Stage II carcinoma of the cervix acquired widespread acceptance about 20 years ago. Many institutions, including our own, developed investigative protocols for the study of this problem. Subsequently, a number of reports have appeared.[1-3,6-17] In 1965, our group described the results in all patients with squamous cell epithelioma who were treated at the Mayo Clinic with irradiation and subsequent radical hysterectomy and pelvic lymph node dissection.[4] In the present report, only patients with Stage I or Stage II lesions are considered; besides patients with squamous cell epithelioma, this includes those with lesions of the cervical stump, those with adenocarcinoma or adenoacanthoma of the cervix, and those who did not receive full radiation therapy for various reasons. Thus, this report represents all patients with Stage I or II cancer of the cervix who were seen for primary therapy of their malignancy between January 1, 1950, and December 31, 1954.

The initial evaluation of the patient included a thorough medical history and physical examination. The laboratory tests comprised those usual to such an evaluation as well as excretory urography and proctoscopic examination. The clinical staging of the lesion was done by both a gynecologist and a radiation therapist.

MATERIAL

From 1950 through 1954 a total of 462 patients received primary therapy for carcinoma of the cervix; 412 had squamous cell carcinoma and 50 had adenocarcinoma or adenoacanthoma. All patients were Caucasians. Of the total, 114 patients received full irradiation and radical surgery, 173 patients were treated with irradiation alone, and 57 patients had surgery as their primary mode of therapy (Table I).

Patients selected for combined therapy were younger than those selected for either of the other modes of therapy (Table I). Early in the program, it was evident that patients who were selected for sequential radiation therapy and surgery had to be in good general health. This meant that all those with debilitating conditions such as diabetes, cardiac or pulmonary diseases, or obesity were not considered for such therapy. As far as possible, those patients were chosen who, after full radiation therapy, could tolerate radical pelvic surgery. No patient was excluded on the basis of age alone.

As expected, almost all of the squamous cell epitheliomas were high grade, whereas the adenocarcinomas were predominantly low grade (Table II). No specific relationship could be established between the grade of the lesion and survival, as has been frequently noted previously.

THERAPEUTIC REGIMEN

Radiation Therapy.—In the sequential program, the radiation therapy consisted of external roentgen or cobalt 60 teletherapy administered concurrently, with intracavitary radium therapy given by the intensive divided-dose technique.[5] The radium applications were made twice weekly

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From the Mayo Clinic and Mayo Foundation: Section of Obstetrics and Gynecology.

Table I

DISTRIBUTION OF 344 PATIENTS WITH CANCER OF THE CERVIX ACCORDING TO TREATMENT MODALITY AND STAGE OF LESION

Stage	Radiation Therapy and Surgery	Radiation Therapy	Surgery	Total
		Squamous cell epithelioma		
I	44 (43.6 yr.)* (23–64)	56 (50.3 yr.)* (29–70)	37 (45.1 yr.)* (23–68)	137
II	64 (43.6 yr.)* (27–58)	104 (53.1 yr.)* (21–79)	12 (46.3 yr.)* (33–74)	180
Total	108	160	49	317
		Adenocarcinoma		
I	3 (51.6 yr.)† (35–67)	4	6	13
II	3 (56.6 yr.)† (23–75)	9	2	14
Total	6	13	8	27
Total	114	173	57	344

* Mean age and age range.
† Mean age and age range for all patients with adenocarcinoma.

during approximately a 4 week period. In the 3 to 4 days between radium applications, the patient was ambulatory. An effort was made to obtain homogeneous irradiation along the entire birth canal. The 50 mg. platinum filtered tube was placed in the proximal portion of the cervical canal for 10 to 14 hours at each of the first two treatments, the posterior wall being packed well away from the radium to secure protection for the rectum. In the third and fourth treatments, also of 10 to 14 hours' duration, the tube was placed in the deeper part of the cervical canal. A tandem was introduced into the uterine cavity at the fifth radium treatment, two 50 mg. tubes being used for 20 to 24 hours. Roentgen or cobalt 60 therapy, which was given concurrently, was omitted on this day. The final three treatments were given in the vaginal cavity, the 50 mg. tube being enclosed in a plastic cylinder of appropriate size. The cylinder was placed transversely first across the face of the cervix, then in the right vaginal fornix, and finally in the left vaginal fornix; the treatment time in each instance was 10 to 14 hours.

Thus, a complete course of treatment for a small lesion in a patient with a small vaginal cavity would total about 5,500 mg.-hr. in 4 weeks; a resistant carcinoma would receive a minimum of 7,300 mg.-hr. Point A received at least 7,000 gamma roentgens, and point B received at least 2,000 gamma roentgens in a large tumor with full dosage.

For the patients receiving sequential therapy, the roentgen therapy was given to two anterior and two posterior pelvic portals, with midline protection between

Table II

DISTRIBUTION OF 344 PATIENTS WITH CANCER OF THE CERVIX ACCORDING TO TREATMENT MODALITY, GRADE (BRODERS'), AND STAGE OF LESION

Stage	Radiation Therapy and Surgery		Radiation Therapy		Surgery	
	Grade	No. of Patients	Grade	No. of Patients	Grade	No. of Patients
			Squamous cell epithelioma			
I	2	5	2	8	2	11
	3	33	3	39	3	22
	4	6	4	9	4	4
II	2	14	2	27	2	4
	3	42	3	62	3	7
	4	8	4	15	4	1
			Adenocarcinoma			
I	1	1	1	1	1	2
	2	1	2	2	2	1*
	3	1	4	1	4	3
II	1	1	1	3	1	2
	2	1*	2	4*	0	0
	4	1*	3	1*	0	0
		6	4	1*	0	0
Total		114		173		57

* One adenoacanthoma.

adjacent zones. Daily treatments of 200 r (air) were delivered at a distance of 50 to 70 cm. to each of two ports, for a total dose of 2,000 to 2,400 r per port, employing 250 kv. with a half value layer of 1.3 mm. of copper. If teletherapy with cobalt 60 was employed, a midplane pelvic dose of 3,500 to 3,700 r was delivered.

After the radiation therapy had been completed, the patient returned in 6 weeks to 3 months—occasionally longer. Then an interim history was obtained and a pelvic re-evaluation was made. Routine laboratory tests were obtained, and the patient was prepared for operation.

Surgery.—The technique of radical hysterectomy and lymph node dissection at this institution has been described by Welch and associates.[18] Briefly, it consists of the complete stripping of areolar, lymphoid, and fatty tissue from the common, external, and internal iliac vessels, the obturator fossae, and the internal femoral ring. This tissue is not removed in one segment, nor is it necessarily removed en bloc with the uterus. Radical hysterectomy, including removal of both tubes and ovaries, follows. The parametrial and paravaginal tissues are severed as close to the pelvic walls as possible, and approximately 3 to 5 cm. of vagina are removed. After removal of the reproductive organs, all surfaces are reperitonealized, utilizing the redundant sigmoid colon for part of this procedure.

RESULTS

Although the 5 and 10 year survival rates of the three groups indicate that surgery alone may be the best method of therapy for Stage I cancer of the cervix (Table III), further analysis reveals that of patients with Stage I cancer treated by primary surgery, 18 of 37 were classified as having microinvasion or very early lesions. There were no patients with Stage I cancer treated by irradiation and surgery or by irradiation alone who had microinvasion or early lesions.

If the 18 patients with microinvasion are subtracted from the group of 37, the survival rate for the remaining 19 patients is 89.5 per cent at 5 years, or almost exactly the same as that in the Stage I group

treated with irradiation and subsequent radical surgery.

Of the 37 patients, 32 underwent the Wertheim procedure, 3 had total abdominal hysterectomy, and 2 had vaginal hysterectomy. Eight patients received postoperative radiation therapy either to the pelvis or to the vaginal vault, or to both. There was one operative death. Two patients were pregnant: 1 patient at 4 months' gestation and another at 6 months' gestation.

Of the 5 patients with adenocarcinoma and 1 with adenoacanthoma treated by surgery primarily, 2 had microinvasion of the cervix. Of these 6 patients, 3 underwent the Wertheim procedure, 2 had total abdominal hysterectomy, and 1 had excision of the cervical stump. Four patients had postoperative radiation therapy.

Table III

SURVIVAL DATA ACCORDING TO TREATMENT MODALITY AND STAGE OF LESION FOR 344 PATIENTS WITH CANCER OF THE CERVIX

Stage	Total No. of Patients	Lived 5 Years or More			Lived 10 Years or More		
		Traced	Alive	Per Cent	Traced	Alive	Per Cent
Radiation therapy and surgery (114 patients)							
Patients with squamous cell epithelioma							
I	44 (1 stump)	44	39	88.6	42	36	85.7
II	64 (3 stumps)	64	46	71.9	63	44	69.8
Patients with adenocarcinoma							
I	3	3	3	100.0	3	3	100.0
II	3 (1 stump)	3	1	33.3	3	1	33.3
Radiation therapy alone (173 patients)							
Patients with squamous cell epithelioma							
I	56 (6 stumps)	54	36	67.4	54	34	63.7
II	104 (5 stumps)	102	60	58.8	98	55	55.1
Patients with adenocarcinoma							
I	4 (1 stump)	4	3	75.0	4	0	0.0
II	9	8	2	25.0	8	2	25.0
Surgery alone (57 patients)							
Patients with squamous cell epithelioma							
I	37 (2 stumps)	37	35	94.6	37	34	91.9
II	12 (3 stumps)	12	7	58.3	12	6	50.0
Patients with adenocarcinoma							
I	6 (1 stump)	6	6	100.0	6	5	83.3
II	2 (1 stump)	2	0	0.0	2	0	0.0

Of the 44 patients treated by irradiation and surgery for Stage I cancer of the cervix, all completed the planned course of irradiation and underwent radical hysterectomy and lymph node dissection. One patient was pregnant at 1 month's gestation. There was one operative death.

Of the 3 patients with adenocarcinoma, all received radiation therapy as planned, with subsequent radical hysterectomy and lymph node dissection.

Of the 56 patients with Stage I cancer of the cervix treated by irradiation, 2 underwent Wertheim procedures that were unsuccessful. One patient had dense adhesions, and 2 patients had all the aortic lymph nodes involved. Various medical contraindications to surgery were noted, including obesity, hypertension, rheumatic heart disease, recent coronary occlusion, diabetes, pyometra after the irradiation, recent thrombophlebitis, and refusal of the patient in 2 instances. Also, a few patients did not undergo surgery subsequent to radiation therapy because of disaffection of some of the physicians with the program of investigation toward the end of the 5 year period. No patients in this group were pregnant when treated.

All 4 patients with Stage I adenocarcinoma of the cervix received adequate radiation therapy; 1 patient had cardiac failure.

Of the 12 patients with Stage II cancer of the cervix treated with primary surgery, 6 received postoperative radiation therapy. In 1 patient the cancer was confined to the cervix, and what clinically seemed to be extension was found at surgery to be endometriosis. One patient had a vaginal hysterectomy performed because of complete prolapse. There were no pregnant patients in this group.

Two patients with Stage II adenocarcinoma were treated by primary surgery. One patient received postoperative radiation therapy.

Sixty-six patients with Stage II cancer of the cervix received radiation therapy and surgery according to the sequential plan. One of the patients had the radical hysterectomy and lymph node dissection performed at another institution. In 1 patient the cancer was associated with pregnancy. Two patients had lesions classified as radiation resistant because the lesions actively grew during radiation therapy.

One patient with Stage II adenocarcinoma of the cervix and 2 with adenoacanthoma were treated by sequential radiation therapy and surgery.

One hundred and four patients with Stage II cancer of the cervix were treated with radiation therapy alone. Five patients in this group underwent Wertheim procedures that were unsuccessful. The same group of medical difficulties appeared as in the Stage I group treated by radiation therapy alone but, additionally, severe osteoporosis and psychopathic personality also were given as contraindications to surgery.

Six patients with adenocarcinoma and 3 with adenoacanthoma (all with Stage II lesion) were treated with radiation therapy alone. One patient was pregnant (2 months), 1 was schizophrenic, and 1 had a concurrent carcinoma of the breast with involved axillary lymph nodes.

COMPLICATIONS OF THERAPY

The incidence of complications resulting from treatment was an important factor in the evaluation of the program. The complications resulting from the use of sequential radiation therapy and radical surgery are shown in Table IV. Only major complications are listed. There was 1 operative death in this group. No deaths were directly related to radiation therapy. There were 16 patients with problems of the urinary tract. The over-all incidence of urinary tract fistula was 7.4 per cent. Massive, brawny lymphedema of the legs and pelvis was seen in 14 of the 108 patients. This was a peculiarly disabling condition that was chronic and most difficult to treat; rarely did it completely resolve. Edema of a minor degree was not included since some edema was seen in almost all patients. Nor was the postoperative loss

TABLE IV

COMPLICATIONS OF THERAPY ACCORDING TO TREATMENT MODALITY AND TYPE OF LESION IN 344 PATIENTS WITH CANCER OF THE CERVIX

Stage	Vascular	Genitourinary	Intestinal	Other
		Radiation therapy and surgery (114 patients)		
I	(14 patients) 8 lymphedema 1 postoperative phlebitis 1 infected hematoma 4 lymphocysts	(4 patients) 1 nephrectomy, vesicovaginal fistula 1 right ureteral stricture 2 urinary retention, severe, chronic	(2 patients) 1 postoperative evisceration 1 massive bowel hemorrhage with death	None
II	(11 patients) 6 lymphedema of legs, thighs, pelvis 2 lymphocysts 2 deep thrombophlebitis 1 pelvic cellulitis	(12 patients) 4 vesicovaginal fistulas 2 rectovesicovaginal fistulas 1 ureterovaginal fistula 2 ureteral repair, postoperative 1 ureteral stricture 1 left nephrectomy for ureteral obstruction 1 bilateral ureteral obstruction with nephrostomies	(7 patients) 1 volvulus of cecum, postoperative 1 intestinal obstruction, postoperative 3 bowel obstruction, postopertive 1 rectovaginal fistula 1 radiation ulceration with resection of sigmoid	(2 patients) 1 psoas abscess 1 pelvic abscess
		Radiation therapy alone (170 patients)		
I	None	(2 patients) 1 urethral stricture 1 factitial cystitis	(2 patients) 2 factitial enteritis requiring colostomy	None
II	None	(4 patients) 3 factitial cystitis 1 injury to ureter with nephrectomy	(5 patients) 4 factitial proctitis 1 factitial sigmoiditis requiring bowel resection	(1 patient) 1 radionecrosis right hip with fracture
		Surgery alone (57 patients)		
I	(4 patients) 2 lymphocysts 2 lymphedema	None	(1 patient) 1 chronic ileus	None
II	(3 patients) 2 lymphedema 1 deep thrombophlebitis	(1 patient) 1 left hydronephrosis and nonfunctioning right kidney	None	None

of bladder sensation considered a major problem because sensation usually returned in 6 months to 1 year.

Table IV lists the major complications after radiation therapy alone; the factitial changes noted were only those severe enough to require prolonged active therapy. Table IV also delineates the complications after primary surgical therapy; there was also one operative death in this group.

Thus, the incidence of major complications after sequential radiation therapy and surgery was 48.1 per cent (108 patients had 52 complications). After radiation therapy alone, 160 patients had 14 major complications, an incidence of 8.7 per cent. After surgery alone, 49 patients had 9 major complications, an incidence of 18.4 per cent.

SEQUENTIAL RADIATION THERAPY AND RADICAL SURGERY

If there is an advantage to combining the two major treatment modalities it should be evident in those patients salvaged by surgery when residual disease was found after radiation therapy was given (Table V). Twenty patients had what appeared to be active disease in the cervix or the pelvic lymph nodes after radiation therapy. Nine of these patients were salvaged. But, 3 patients with Stage I cancer and 6 patients with Stage II cancer who did not have residual disease at radical surgery died from recurrent carcinoma of the cervix within 6 years of the start of therapy.

COMMENT

This presentation is a study of frustration in clinical experimentation. It was hoped at the onset that a definite conclusion could be established in regard to combining adequate radiation therapy and radical surgery for Stage I and II cancer of the cervix. However, it is apparent that of the 317 patients with squamous cell epithelioma available for study only one third were actual candidates for such combined therapy. Also, it was certainly reasonable to exclude those patients with microinvasion because sequential therapy would have been overtreatment for these highly curable lesions, and it would be unfair to subject patients already suffering from major medical complications to the increased hazards of combined therapy. Many patients, however, did not undergo combined therapy because of less cogent reasons, including disaffected clinicians and disillusioned surgeons who had faced the rigors of frequent postoperative complications in the patients in whom radiation therapy had preceded the operation.

The three groups remaining from this selection process cannot be compared with each other or with patients treated at other time intervals. Certain conclusions, it would seem, can be drawn. These are:

(1) There is an increased incidence of complications after sequential radiation therapy and surgery: 48.1 per cent *versus* 18.4 per cent for surgery alone and 8.7 per cent for radiation therapy alone.

(2) Although the survival rates are apparently higher for patients undergoing surgery alone and for those treated by irradiation and subsequent surgery than for patients undergoing irradiation alone, selection of patients in this series placed the poor-risk patient in the irradiation alone category.

(3) An occasional patient can be salvaged by combining radiation therapy and surgery but, at present, there is no technique available to accurately select this patient.

(4) Judicious use of radiation therapy alone, or surgery alone, affords equal opportunity for survival to patients with Stage I or II cancer of the cervix.

SUMMARY

Four hundred and sixty-two patients received primary therapy for cancer of the cervix at the Mayo Clinic from 1950 through 1954. Four hundred and twelve had squamous cell epithelioma and 50 had adenocarcinoma or adenoacanthoma. One hundred and fifty patients had Stage I cancers, whereas 194 had Stage II cancers. Of these 344 patients, 114 were treated by

TABLE V

STATUS OF PATIENTS UNDERGOING SEQUENTIAL RADIATION THERAPY AND SURGERY WHO HAD RESIDUAL CANCER IN CERVIX OR LYMPH NODE METASTASIS

	Residual cancer in cervix (outcome and status)	
Stage I	(1 patient)	
	No complications	Alive
Stage II	(6 patients)	
	Residual cancer, 10 by 5 by 5 mm.	Alive
	No complications	Alive
	Left ureterovaginal fistula	Alive
	Lesion, 7 by 5 cm. (radiation resistant)	Dead
	Vesicovaginal fistula (radiation resistant)	Dead
	Intestinal obstruction	Dead
	Lymph node metastasis (location of involved lymph node and status)	
Stage I	(4 patients)	
	Left obturator lymph node	Alive
	Bilateral obturator lymph nodes	Alive
	Left iliac lymph node	Dead
	Iliac and aortic lymph nodes (2 cm. above bifurcation)	Dead
Stage II	(9 patients)	
	Left external iliac lymph node	Alive
	Right external iliac lymph node	Alive
	Obturator lymph node	Alive
	Bilateral obturator lymph nodes	Dead
	Left iliac lymph node and left pelvic wall	Dead
	Iliac lymph node (pulmonary metastasis, 3 mo.)	Dead
	Left iliac lymph node (pulmonary metastasis, 17 mo.)	Dead
	Iliac and obturator lymph nodes (pulmonary metastasis, 14 mo.)	Dead
	Bilateral iliac and obturator lymph nodes	Dead

full irradiation with subsequent radical surgery, 173 by irradiation only, and 57 by surgery alone.

The 5 and 10 year gross survival rates for Stage I showed that survival was best for surgery alone (94.6 and 91.9 per cent, respectively), radiation therapy with surgery was next (88.6 and 85.7 per cent, respectively), and radiation therapy alone was third (67.4 and 63.7 per cent, respectively). However, further analysis showed that the survival rates for surgery alone and radiation therapy with surgery were almost identical when the patients with microinvasive lesions of the cervix were not included. Furthermore, the poor-risk patient was most frequently included in the group that received radiation therapy alone.

In patients with Stage II lesions, radiation therapy with surgery resulted in a better survival at 5 and 10 years (71.9 and 69.8 per cent, respectively), whereas the survival rates for radiation therapy alone (58.8 and 55.1 per cent) and for surgery alone (58.3 and 50.0 per cent) were nearly identical. Again the poor-risk patient was found in the group of patients who received radiation therapy alone.

The high incidence of major complications in the patients treated by radiation therapy and subsequent surgery was discouraging. Thus, in cancer of the cervix, surgery alone is somewhat preferable in Stage I and radiation therapy alone is preferable in Stage II. However, individualization of the treatment for each patient according to general health and type of

malignancy still remains the most important factor in treatment.

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MANAGEMENT OF STAGE I AND II ADENOCARCINOMAS OF THE UTERINE CERVIX ON INTACT UTERUS*

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ADENOCARCINOMAS of the uterus can originate in the endometrium and can be clearly diagnosed as being of corporeal origin. They can be shown by fractional curettage to be present both in the endometrium and endocervix and are then diagnosed as adenocarcinoma of the corpus et collum. The adenocarcinomas which, after careful fractional curettage, seem to originate only in the cervix will be the subject of this paper.

Survival rates for patients with adenocarcinomas of the cervix, when compared with those for squamous cell carcinomas, vary considerably from series to series. The prevailing opinion is that the adenocarcinomas are not as readily controlled by radiotherapy, although there are series where the survival rates are close to those for patients with squamous cell carcinomas.

These differences in survival rates may be related to the care with which one rules out involvement of the corpus, as obviously a patient treated by radiotherapy for a cervical adenocarcinoma with involvement of the corpus must have different management than the patient without such involvement.

MATERIAL AND POLICIES OF TREATMENT

Between 1948 through December 1963, 1,412 patients with Stage I and Stage II cervical cancers on intact uterus were treated at M. D. Anderson Hospital. In 1,341 patients the histology was squamous cell carcinoma and in 71 patients, adenocarcinoma.

With the exception of 3 patients, 1 with Stage I and 2 with Stage II_A lesions, who were treated by primary hysterectomy and lymphadenectomy, all patients were treated by radiotherapy only or by radiotherapy followed by conservative total hysterectomy alone, or by radiotherapy followed by hysterectomy and lymphadenectomy. Radiation techniques for cervical adenocarcinomas are similar to those used for squamous cell carcinomas except that when a hysterectomy is planned, the radiation dose is slightly diminished.

It has been a practice through the years to use increasingly the addition of hysterectomy whenever the patient is suitable for the operation, because of the general belief expressed in the literature that radiation therapy may not be as effective for adenocarcinomas as for squamous cell carcinomas and that, being as a rule of endocervical origin, the adenocarcinomatous lesions are, stage for stage, bulkier than are the squamous cell carcinomas because of the enlargement of the endocervix and isthmus. Irradiation is completed first, and a 4 to 6 week interval is allowed before the hysterectomy is performed. For a certain period of time, lymphadenectomies were also part of the treatment plan.

The hysterectomy is conservative; the uterus is removed without an additional vaginal cuff, with minimum dissection of

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Table I

THREE- AND FIVE-YEAR ABSOLUTE SURVIVAL OF PATIENTS WITH STAGE I AND II ADENOCARCINOMAS OF THE CERVIX ON INTACT UTERUS

(1948 through December 1963)

Stage		Radiotherapy Alone	Radiotherapy Plus Surgery	Total Group Per Cent
I	3 years	8/9	17/21	83.3 (25/30)
	5 years	7/8	10/11	94.4 (17/19)
II_A	3 years	6/10	12/13	78.2 (18/23)
	5 years	2/6	6/7	61.5 (8/13)
II_B	3 years	5/8	6/9	64.7 (11/17)
	5 years	5/7	4/6	69.2 (9/13)
Total	5 years	14/21	20/24	75.0 (34/45)

the bladder, ureters, and rectosigmoid colon. As much tissue as possible is removed with the cervix, without dissecting the ureters from their paracervical position. The conservative procedure has few complications and should be adequate to remove any residual cancer remaining within the myometrium. The procedure supplements the irradiation which gives an adequate dose to the vaginal mucosa and the paracervical area, but which may be somewhat inadequate in reaching cancer cells deep in the myometrium.

RESULTS

The 3 patients treated by primary surgical resection died within 2 years because of pelvic recurrences of the disease. Coincidentally, in 2 of these patients, disease involved the ovaries.

The results will be presented by comparing the two groups of patients, one of which was treated by irradiation alone, and the other with irradiation followed by hysterectomy. The conclusions are tempered by the facts that: (1) the numbers are small, and (2) the two groups are not entirely comparable because some patients in the first group were not suitable for surgical resection, and hence had a high risk of death from intercurrent disease.

Three- and five-year survival rates for the two groups are given in Table I. The survival rates for the whole group are as good as those for squamous cell carcinomas. The 5-year survival rate for the patients treated with irradiation alone is 66 per cent; for those treated with irradiation and surgery, 84 per cent; and for the whole group, 75 per cent. However, one can see from Table II, which gives the sites of active disease, that 24 per cent of the patients in the irradiation only group, and 22 per cent of the patients in the irradiation followed by hysterectomy group, died from disease. In both groups, central failures are rare. The incidence of failure to control disease in the pelvic area in the irradiation alone group is slightly higher than is the incidence of failure in the irradiation and surgery group.

In the entire group of patients with adenocarcinoma of the cervix, 32 lymphadenectomies were done; 26 were Stage I and Stage II patients and 6 were Stage III patients. In only 1 patient were the regional lymphatics involved. In addition, periaortic lymph nodes were involved in 2 patients. Even if one considers that irradiation had been given before the lymphadenectomy, this is a very low incidence of involvement. The complications resulting from the surgical technique performed after radical irradiation are significantly greater when a lymphadenectomy is done. Therefore, the lymphadenectomy procedure in addition to conservative hysterectomy has been discontinued.

DISCUSSION

The data presented do not show a clear-cut advantage for addition of hysterectomy after irradiation for adenocarcinoma of the cervix. However, although the numbers are too small for statistical significance, there does seem to be some difference in patterns of growth and spread of the adenocarcinomas of the cervix as compared to those for

Table II

SITES OF ACTIVE DISEASE AT TIME OF DEATH OF PATIENTS WITH STAGE I AND II ADENOCARCINOMAS OF THE CERVIX ON INTACT UTERUS

(1948 through December 1963)

Stage and Treatment	No. of Patients Treated	Dead of Cancer	DM Only	Local Only or +PD +DM	Pelvic Only or +DM
Radiotherapy Alone					
I	9	0	0	0	0
II_A	9	3	2	1	0
II_B	7	3	0	0	3
Subtotal	25	6	2	1	3
Radiotherapy Plus Surgery					
I	21	3	1		2
II_A	13	2	1	1	0
II_B	9	4	2	2	0
Subtotal	43	9	4	3	2
Total	68	15	6	4	5

DM—Distant Metastases (metastases beyond region of pelvic cavity and regional lymphatics).
PD—Pelvic Disease (adenocarcinoma within region of pelvic cavity and regional lymphatics).

the squamous cell carcinomas. A case can be made for adding hysterectomy in some cases for the following reasons:

(1) Adenocarcinomas are, as a rule, of endocervical origin and grow to large lesions at the level of the endocervix and isthmus. This pattern of local growth allows them to remain longer in Stage I and II than do the squamous cell carcinomas.

(2) Invasion into the myometrium is common; spread to the regional lymphatics is infrequent. Failures have been because of recurrent disease in the lower vagina or other pelvic structures, but not in the regional lymphatics. For squamous cell carcinomas, the most common cause of failure within the irradiated area is because of lymph node involvement which is evidenced clinically by leg edema, sciatic pain, and hydronephrosis.

(3) A selected group of patients with endocervical bulky squamous cell carcinomas have been submitted to an additional hysterectomy. There is a difference in the incidence of observed residual disease in the surgical specimen: 41 per cent in the adenocarcinoma group as compared with 30 per cent in the squamous cell carcinoma group. In some instances, in both groups, cancer might not have been viable, but the difference in morphologically residual disease may mean that there is more often invasion of the myometrium by the adenocarcinomas than by the squamous cell carcinomas.

Seven patients with Stage I and II adenocarcinoma on the cervical stump have been treated by radiotherapy only. One patient with Stage II_B disease died at 2 years with local and pelvic disease. Of the other patients, 1 died at $5\frac{1}{2}$ years because of mediastinal metastases and 5 are alive from 5 to 12 years after treatment. It seems to indicate that the absence of the corpus is significant in the prognosis because its absence gives no opportunity for spread of disease to the myometrium.

If no lymphadenectomy is performed, the complications of added conservative hysterectomy are minimal. Therefore, whenever one is dealing with an endocervical and somewhat bulky lesion, the uncer-

tainty of how much of the myometrium is involved justifies an added conservative hysterectomy which may add to the effectiveness of the treatment.

SUMMARY

Irradiation alone or very slightly diminished irradiation followed by conservative hysterectomy has produced 75 per cent 5-year survival rates in Stage I and II adenocarcinomas of the cervix which are as good as the 5-year results for squamous cell carcinomas. Primary irradiation carried to the fullest or near fullest is to be maintained; but because of the usual endocervical origin and the tendency to invade the myometrium in the patients who have a bulky endocervical lesion, the addition of a conservative hysterectomy may increase the chances of cure.

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RADIOTHERAPY FOLLOWING SIMPLE HYSTERECTOMY IN PATIENTS WITH STAGE I AND II CARCINOMA OF THE CERVIX*

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THE purpose of the author is to answer the question, "Should elective postoperative radiotherapy be given following simple hysterectomy for early (presumed Stage I and Stage II) carcinoma of the cervix?" Cosbie[1] has reported a group of patients who had radiotherapy after simple hysterectomy in the presence of undetected carcinoma of the cervix or as the intended treatment for carcinoma of the cervix. His series consisted of 59 patients with a 3-year survival rate of 76 per cent and a 5-year survival rate of 71 per cent. Treatment in this group of patients was largely external radiotherapy plus local therapy to the vaginal apex.

PATIENT MATERIAL

All patients who had a simple total hysterectomy for, or in the presence of, carcinoma of the cervix and who were referred for radiotherapy after operation from 1948 through 1963 were reviewed. In most of these patients, the operation was performed for a benign lesion, and the finding of invasive carcinoma was unexpected. A few patients had hysterectomy for carcinoma *in situ*, and invasive carcinoma was actually found in the surgical specimen. A small number had hysterectomy as the intended treatment for an early carcinoma of the cervix. All patients who had evidence of invasive carcinoma but who had no gross residual disease following surgery were selected for study. The 54 patients available for 3-year analysis were divided into 3 groups (Table I). Patients with known residual or recurrent disease at the time of admission are excluded from this report.

Table I

PATIENT CATEGORIES

Group I (18 patients) Patients with microscopic evidence of invasive cancer found incidentally in hysterectomy specimen
Group II (25 patients) Gross tumor in the surgical specimen with apparent surgical clearance
Group III (11 patients) Tumor cut through at the margins of surgical resection but no known gross residual disease

TREATMENT

The majority of patients treated during the years 1948 to 1954 (5 of 9) received local therapy alone: usually 2 applications of radium in vaginal ovoids delivering a surface dose to the vaginal apex of between 8,600 and 14,400 r. The remaining 4 patients received 2,000 to 4,500 r whole pelvis irradiation at 250 or 400 kvp., and local therapy to the vaginal apex using ovoids or transvaginal therapy at 140 kvp.

In 1954, an Allis Chalmers 22 mev. betatron became available. Since that time an increasing number of the patients have received some whole pelvis irradiation (up to 5,000 rads in 5 weeks) supplemented by therapy to the vaginal apex using either

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Table II

SURVIVAL AT 3 AND 5 YEARS

Group	Follow-up	Number Treated	Alive	Dead	
I Microscopic disease only in specimen	3-year follow-up	18	18		
	5-year follow-up	16	15	1	Lost to follow-up; NED at 3+ years
II Gross disease in specimen	3-year follow-up	25	23*	2	Dead of disease
	5-year follow-up	17	14†	3	Dead of disease
III Microscopic cut-through of disease	3-year follow-up	11	11		
	5-year follow-up	9	9‡		

* There were 3 subsequent deaths because of disease at 5, 8, and $8\frac{1}{2}$ years.
† There were 2 subsequent deaths because of disease at 8, and $8\frac{1}{2}$ years.
‡ There was 1 subsequent death because of disease at $8\frac{1}{2}$ years.
NED—No evidence of disease.

vaginal ovoids or transvaginal therapy in varying amounts.

RESULTS

The number of patients surviving 3 and 5 years is shown in Table II, and the causes of death at any time of follow-up are shown in Table III. There were 54 patients treated 3 or more years ago and 42 patients treated more than 5 years ago.

All 18 patients in Group I were without evidence of disease at 3 years. Of the 16 patients available for 5-year analysis, all were without evidence of disease between 3 and 5 years, except for 1 patient lost to follow-up without evidence of disease. No patients developed late recurrent disease after 5 years.

Of the 25 patients in Group II followed for 3 years or more, 2 died in less than 3 years, 1 of distant metastases with local pelvic control and 1 of local recurrence. One of the patients who had no evidence of disease at 3 years developed a vaginal recurrence at $3\frac{3}{4}$ years and expired 5 years after treatment. Two patients subsequently died of cancer 8 and $8\frac{1}{2}$ years after treatment, 1 of pelvis recurrence and 1 of distant metastasis with pelvic control. One patient expired at 7 years of malignant lymphoma with apparent control of her initial primary tumor The remaining patients are living and well without disease up to 15 years.

All of the 11 patients in Group III were without evidence of disease at 3 years and the 9 patients who were available for 5-year analysis were all without evidence of disease at 5 years. One patient subsequently expired of vault and pelvic recurrence at $8\frac{1}{2}$ years.

The complications of treatment were minimal. One patient developed a rectal stricture requiring a colostomy, and a second patient required a local resection of the ileum for radiation stenosis.

DISCUSSION

The strikingly good results in the 3- and 5-year survival rates in these 3 groups of

Table III

CAUSES OF DEATH AT ANY TIME OF FOLLOW-UP

Group	Dead	Pelvic Disease	Distant Metastases Only	Intercurrent Disease
I Microscopic disease only in specimen	1			1
II Gross disease in specimen	6	3	2	1
III Disease cut through at margin of resection	1	1		

patients are interesting from several points of view. At first glance, they appear superior to the results of treating patients with early carcinoma of the cervix by surgery or radiotherapy alone. However, this undoubtedly reflects the selectivity involved in a group of patients such as this. By and large, these were young (average age 46 years), healthy patients; the old, bad-risk patients were automatically eliminated. Thus there has been very little loss because of intercurrent disease.

The substantial number of patients with preclinical or clinically undetectable disease tends to weigh the results favorably. All patients with residual lateral parametrial involvement or metastatic disease in regional lymph nodes were excluded from this series. Thus, in a sense, this does represent a surgically staged group of patients with relatively early carcinoma of the cervix who were referred for immediate postoperative radiotherapy. The good results reflect considerable bias in patient material and should not be construed as suggesting the superiority of treating patients with early but clinically evident carcinoma of the cervix by simple hysterectomy followed by radiotherapy.

The proponents of surgery as the treatment of choice for carcinoma of the cervix have cited late central recurrences as a point in favor of surgical treatment, arguing that if the uterus had been removed, the late recurrence would have been prevented. The 4 central recurrences in our series, as late as $8\frac{1}{2}$ years after treatment, show that late recurrences can occur even if the uterus has been removed.

The good results at 3 and 5 years should be contrasted with the poor results in a group of patients with recurrent disease who were treated more than 6 months after hysterectomy; all patients were dead within 3 years except those who presented with localized central recurrence at the vaginal apex.[2]

While a randomized study has not been performed, and some of the patients in this study may not have needed treatment at all, the good results and low complication rate and the poor results once recurrent disease has become evident suggest that elective postoperative radiotherapy should be offered to all patients with invasive carcinoma of the cervix who present after hysterectomy.

Table IV summarizes the current treatment plan and Table V gives the usual dosage combinations of whole pelvis irradiation and local vaginal therapy, either by intracavitary radium or transvaginal therapy.

The results in the early cases seem to reveal that almost all patients have done uniformly well irrespective of whether they had local therapy alone, or whole pelvis irradiation followed by local therapy. The trend during recent years to treat all patients referred for radiotherapy fol-

Table IV

GENERAL TREATMENT PLAN

Group	
I	Local irradiation to the vaginal apex using intracavitary radium in ovoids or transvaginal therapy
II	Whole pelvis irradiation to 3,500 to 4,000 rads followed by 2 48-hour radium applications, 1 to 2 weeks apart
III	Whole pelvis irradiation to 5,000 rads followed by one 72-hour radium application in ovoids

lowing hysterectomy with whole pelvis irradiation has not been associated with significant morbidity and complications. However, if one is able to obtain the clinical and pathologic information necessary to separate the early cases, local therapy alone appears to be sufficient for that group. This can be administered with vaginal ovoids alone, usually in 2 72-hour insertions 2 weeks apart, using the standard loading for the ovoids (*i.e.*, 25 mg. of radium in large ovoids, 20 mg. of radium in medium ovoids, and 15 mg. of radium in small ovoids). This will give a surface dose of 11,000 to 13,000 rads to the vaginal apex. If the anatomic situation is unfavorable for radium, 6,000 rads may be administered using transvaginal therapy at 140 kvp., usually at the rate of 500 rads daily. Also, if there appears to be considerable thickness to the induration at the vaginal apex, a larger depth dose can be delivered with the transvaginal cone than with vaginal radium.

Patients in Group II with more advanced disease and patients in Group III who have known cut-through of tumor require a greater percentage of their treatment with whole pelvis irradiation because of the increased risk of pelvic contamination or undetected regional lymphatic disease. If they receive 3,500 to 4,000 rads tumor dose to the entire pelvis, the surface dose from vaginal radium should be reduced to 7,000 to 8,000 rads. This can be accomplished by 2 48-hour insertions of vaginal ovoids using the above loadings. The transvaginal dose should be limited to 4,000 rads. After 5,000 rads whole pelvis irradiation, the local treatment to the vaginal apex should be limited to one 72-hour insertion of radium in vaginal ovoids delivering a surface dose of 5,000 to 6,000 rads, or 3,000 rads using transvaginal therapy. If the local anatomy is unfavorable for either radium or transvaginal therapy, 5,000 rads whole pelvis irradiation can be given in 5 weeks, followed by an additional 1,000 to 2,000 rads given through reduced fields over the vaginal apex.

CONCLUSIONS

1. Immediate postoperative radiotherapy in patients with presumably Stage I and II carcinomas of the cervix following simple hysterectomy produces excellent

Table V

DOSAGE COMBINATIONS OF WHOLE PELVIS IRRADIATION WITH INTRACAVITARY OR TRANSVAGINAL THERAPY

Whole Pelvis (tumor dose in rads)	None	2,000–3,500	3,500–4,000	5,000	6,000	7,000
Intravaginal Radium* (surface dose in rads)	72 hr.–72 hr. (11,000–13,000)	72 hr.–48 hr. (8,000–10,000)	48 hr.–48 hr. (7,000–8,000)	72 hr. (5,000–6,000)	48 hr. (4,000)	None
Transvaginal Therapy (given dose in rads)	6,000	4,500–5,000	4,000–4,500	3,000–3,500	2,500–3,000	None

* Times refer to time of ovoid application required to give the specified surface dose at the vaginal apex using the standard loadings of 15 mg.–15 mg. in small ovoids, 20 mg.–20 mg. in medium ovoids, and 25 mg.–25 mg. in large ovoids.

survival rates with very few complications and should be given electively.

2. Very early cases do well with only local therapy to the vaginal apex; more advanced cases require a combination of whole pelvis irradiation and local therapy.

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PERSISTENT TUMOR CELLS IN THE VAGINAL SMEAR DURING THE FIRST YEAR AFTER RADIATION THERAPY OF CARCINOMA OF THE UTERINE CERVIX*

PROGNOSTIC SIGNIFICANCE

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INVASIVE carcinoma of the uterine cervix remains a significant health problem in some communities; at the Radiotherapy Department of the I. González Martínez Oncologic Hospital in San Juan this type of tumor constitutes 20 per cent of the present therapy patient work load.

During the last 20 years radiation therapists have been able to develop safe and efficient techniques for the radiologic treatment of carcinoma of the uterine cervix.

The curability results obtained by radiation therapy in patients with carcinoma of the uterine cervix justify its classification as the treatment of choice for this condition;[1] yet, despite present radiotherapeutic achievements, we fail to cure a significant number of patients. At our Department these treatment failures presently range from 10 per cent in Stage I cases to 55 per cent in patients with Stage III lesions.

The need exists to detect irradiation failures early enough so as to be able to administer additional therapy with a better chance of success; this may be of the nature of a surgical procedure or further irradiation. Present clinical means for the detection of postirradiation treatment failures do not always permit the discovery of early and favorable tumor manifestations; at times, it is most difficult to distinguish recurrent or persistent tumor from post-irradiation normal tissue changes. The use of biopsy material for the detection of post-irradiation persistence presents certain limitations;[5,6] a slowly regressing tumor may be mistaken for a persistent lesion.

The present report relates to a study of the prognostic significance of persistent tumor cells in the vaginal cytology smear during the first year after irradiation for carcinoma of the uterine cervix.

MATERIAL AND METHODS

At the end of 1960 a project was started at the Radiotherapy and Cancer Division of the Puerto Rico Nuclear Center with the aim of determining the value of exfoliative cytology as a prognostic test in patients with carcinoma of the uterine cervix submitted to irradiation. Vaginal smears were taken before, during, and after irradiation. Initially two smears were taken per case (one by scraping the cervix and the other by pipette suctioning of the vaginal pool). In 1964 it was decided that one slide could include both samples and this practice persisted. The smears were processed by the Papanicolaou method for microscopic study for persistent tumor cells and for evidence of radiation effects in the normal epithelium.

For the present analysis we have utilized the cytologic diagnoses of persistent tumor cells in the smears taken 1, 2, 4, 6, and 12 months post irradiation. Besides the initial cytologic impression, all the slides were reviewed again during the last year and the pathologist has relied on his present criteria of what is a tumor cell in the vaginal

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smear after irradiation for carcinoma of the cervix uteri. Cytologic impressions were classified as positive or negative for tumor cells, suspicious for tumor cells, or unsatisfactory.

The patients in this study were mostly of low socio-economic level who were referred to the I. González Martínez Oncologic Hospital for radiation therapy of histopathologically proven carcinoma of the uterine cervix. At times, because of economic reasons, they had difficulty in transportation to the hospital. A total of 342 cases were included in the study with minimal post-treatment follow-up of 3 years. For various reasons, not all cases seen during the study period were included. A few patients were unable to provide a satisfactory cytologic smear, and some, because of economic or other personal reasons, failed to return for follow-up during the first year. The reasons for exclusion were: persistent unsatisfactory vaginal smears; no available vaginal smear in the first post-treatment year; and treatment interruption before an adequate dose was delivered. The excluded cases constitute approximately 30 per cent of the cervical cancer work load in the Department during the time of the study.

Survival and tumor-free status were determined at 3, 4, and 5 years after radiation therapy. Four per cent of the cases could not be traced at the 5-year mark because of change in address or other reasons.

Using follow-up information from the patients' charts, we correlated tumor-free survival with the presence of persistent tumor cells in the vaginal smear after irradiation, taking into consideration the stage of the disease and the treatment modality.

TREATMENT TECHNIQUES

Patients in this study received external irradiation by orthovoltage roentgen therapy (half value layer of 3 to 4 mm. Cu) or cobalt 60 teletherapy, followed by intracavitary therapy. Anterior and posterior pelvic fields were used; the width ranged from 16 to 18 cm. and the height from 12 to 14 cm., depending on the size of the pelvis.

In the first 2 years of the study, roentgen therapy cases were treated by means of sacrosciatic fields, in addition to the anterior and posterior ones. The external irradiation doses were calculated as exposures in the mid-pelvis and ranged from 4,000 r in 6 weeks with roentgen rays to 4,500 r in 6 weeks with cobalt 60. For curietherapy, we utilized radium or cobalt 60 sources in the vagina and the uterus; the doses averaged 4,000 r calculated at point A.

THE IDENTIFICATION OF TUMOR CELLS IN THE POSTIRRADIATION VAGINAL SMEAR

Satisfactory postirradiation vaginal smears may contain benign and tumor cells with or without irradiation effect. The identification of tumor cells without irradiation effect offers no difficulty to the pathologist. Tumor cells with irradiation changes may show: bizarre appearance, giant and multiple nucleoli, marked vacuolization, and increased cell size. Likewise, benign cells may show comparable irradiation changes: increased size of the cell and the nucleus, conspicuous vacuolization, multinucleation, and nuclear changes (pyknosis, karyorrhexis, wrinkling and multiple nucleoli). At times, it may be difficult to differentiate between dysplastic cells and malignant cells, when they show pronounced irradiation changes. Some of these cases are labelled "suspicious."

A number of smears are found unsatisfactory for diagnosis; this may be due to the presence of too many leukocytes, when a purulent discharge is present or to scanty material with practically no identifiable cells.

INCIDENCE OF SMEARS NEGATIVE FOR TUMOR CELLS DURING THE FIRST YEAR POSTIRRADIATION

The number of cases showing smears negative for tumor cells after irradiation, at various post-treatment intervals, is shown in Table 1. This table excludes cases

Table I

PER CENT OF NEGATIVE SMEARS BY MONTHS AFTER THERAPY

Months after Therapy	No. with Satisfactory Smear	Per Cent Negative
1	248	74
2	265	86
4	252	89
6	216	90
12	184	90

which were lost to follow-up and patients with unsatisfactory smears. By the end of 1 month post treatment, 26 per cent of cases showed smears suspicious or positive for tumor cells; this number rapidly decreased to the 10 per cent level found 6 and 12 months post therapy. The number of unsatisfactory smears ranged from 63 at 2 months post therapy to 144 twelve months post irradiation.

TUMOR-FREE SURVIVAL OF THE PATIENTS UNDER STUDY

The tumor-free survival status of all patients in the study, correlated with stage of disease and treatment modality is shown in Table II. The number of Stage I cases is too small for proper statistical evaluation; the 5-year tumor-free survival in this group was 86 per cent for cobalt 60 teletherapy cases and 92 per cent for roentgen therapy patients. Stage II cases had a 5-year tumor-free survival of 80 per cent with cobalt 60 teletherapy and 57 per cent with roentgen therapy. Stage III cases had a tumor-free 5-year survival of 47 per cent with cobalt 60 teletherapy and 21 per cent with roentgen therapy. Stage IV cases in this study had no tumor-free 5-year survivors.

The correlation between presence of a negative smear at different post-treatment months and tumor-free survival for all stages is shown in Table III. The chances of living with no evidence of disease at 3, 4, and 5 years, after a negative smear, are shown in this table. The 5-year tumor-free survival goes up from 43 per cent when the smear is negative 1 month after irradiation to 65 per cent when this condition is found 12 months post treatment. The presence of a negative smear does not appear to be of prognostic significance in the first 4 months post irradiation.

Table IV shows the correlation of the

Table II

SURVIVAL BY TREATMENT MODALITY AND STAGE

Treatment	Stage	At 3 Years		At 4 Years		At 5 Years	
		No. Eligible	% NED	No. Eligible	% NED	No. Eligible	% NED
Cobalt 60	All	173	66	102	65	49*	63
	I	29	90	13	85	7	86
	II	87	69	51	69	20	80
	III	49	53	32	53	19	47
	IV	8	25	6	33	3	0
Roentgen Rays	All	155	51	123	48	91†	44
	I	22	91	17	88	12	92
	II	60	58	46	61	35	57
	III	70	34	57	28	42	21
	IV	3	0	3	0	2	0

* Excluding 2 patients lost to follow-up.
† Excluding 4 patients lost to follow-up.
NED = no evidence of disease.

Table III

RELATIONSHIP OF NEGATIVE SMEAR AND CHANCE OF BEING FREE OF DISEASE

All Stages

Months after Therapy	At 3 Years		At 4 Years		At 5 Years	
	No. Negative	% NED	No. Negative	% NED	No. Negative	% NED
1	183	56	114	49	67	43
2	227	61	60	56	97	52
4	224	63	164	60	105	58
6	194	67	145	61	84	57
12	165	72	122	67	68	65

NED = no evidence of disease.

presence of a negative smear, with tumor free survival for Stage I and II cases together; Table V shows this relationship for Stage III and IV cases. From these tables it appears that a negative cytology report 4 to 12 months post irradiation is associated with a good prognosis in the early stages (73 to 82 per cent tumor-free 5-year survival); however, in Stage III and IV a negative report is not associated with a particularly good prognosis.

The correlation of the presence of a smear positive for tumor cells in the post irradiation period with tumor-free survival is shown in Table VI. The chance of having tumor-free 5-year survival is extremely low

Table IV

RELATIONSHIP OF NEGATIVE SMEAR AND CHANCE OF BEING FREE OF DISEASE

Stage I and II

Months after Therapy	At 3 Years		At 4 Years		At 5 Years	
	No. Negative	% NED	No. Negative	% NED	No. Negative	% NED
1	113	67	63	62	33	64
2	133	75	89	71	52	73
4	138	76	96	75	61	77
6	124	76	87	72	46	74
12	107	82	74	81	39	82

NED = no evidence of disease.

Table V

RELATIONSHIP OF NEGATIVE SMEAR AND CHANCE OF BEING FREE OF DISEASE

Stage III and IV

Months after Therapy	At 3 Years		At 4 Years		At 5 Years	
	No. Negative	% NED	No. Negative	% NED	No. Negative	% NED
1	70	37	51	33	34	24
2	94	41	71	37	45	29
4	86	43	68	40	44	32
6	70	51	58	45	38	37
12	58	53	48	46	29	41

NED = no evidence of disease.

Table VI

RELATIONSHIP OF POSITIVE SMEAR AND CHANCE OF BEING FREE OF DISEASE

Months after Therapy	At 3 Years		At 4 Years		At 5 Years	
	No. Positive	% NED	No. Positive	% NED	No. Positive	% NED
1	49	65	44(1)*	61	40(2)*	65
2	29	45	23	48	21	47
4	18	39	8	38	5	(0)
6	11	36	7	14	5	(20)
12	10	30	5	(20)	3	(33)

* Number of lost cases excluded.
NED= no evidence of disease.

when a smear has been found to contain tumor cells 4 or more months after therapy; however, the number of cases in this portion of the study is too low to justify any valid conclusion.

DISCUSSION

The results of this study show that exfoliative cytology of the vagina, used during the first year after irradiation for carcinoma of the uterine cervix, is of some relative value in the management of these cases when a satisfactory smear is obtained. Unfortunately, the number of smears considered unsatisfactory by the clinician at the time the sample was taken or by the laboratory personnel was high; this was so in 80 cases at 1 month, 63 at 2 months, 76 at 4 months, 112 at 6 months, and 144 at 12 months. The reasons for an unsatisfactory smear may be: excessive inflammatory changes in the vaginal canal, dry mucosa with resulting scanty material in the sample, stenosis of upper vaginal canal, and gross bleeding when adhesions are broken during the examination.

Another limiting factor in the use of this technique relates to the location of the persistent or recurrent disease; a good number of the recurrences are in the parametria or the pelvic wall. An analysis of sites of active disease at the time of death in patients within 5 years after radiation therapy for carcinoma of the uterine cervix at the M. D. Anderson Hospital in Houston, Texas, revealed that in the groups of patients dying with tumor limited to the pelvis, more than 50 per cent had no local disease.[4] Talbert and co-workers[7] have reported that in their cases 20–30 per cent of the recurrences were in the parametria.

Some cases with gross tumor may not have a positive cytology; these false negatives may be as high as 9 per cent.[7] The presence of grossly suspicious tumor on pelvic examination calls for diagnostic studies. Therapy should not be instituted until persistent disease is proven; inflammatory or postirradiation changes may mimic cancer. In a group of 991 cases with the initial diagnosis of recurrent or persistent cervix cancer at Memorial Hospital in New York, 14 per cent did not have cancer.[2]

The persistence of tumor cells in the smear in the first months post therapy has no significance. This finding becomes important at 4 months or later. This experience is different from that reported by Koss[3] who states that the presence of cancerous cells for a period of 4 weeks following the completion of radiation treatment for cervical cancer carries an ominous prognosis. The time of disappearance of the tumor cells from the smear is related to the rate of regression of the tumor after radiation therapy. It is well known that some tumors have very long volume doubling times, and consequently would grow or disappear very slowly. Although by the end of the first postirradiation month 75 per cent of cases will have negative smears,

some cases will have persistent tumor cells 6 or 12 months post therapy and never show further evidence of disease. The finding of malignant cells in the smear up to 1 year after successful radiation therapy has also been reported by Von Haam and Albery.[8]

Regardless of the above mentioned exceptions, when we find persistent tumor cells 4 months or longer after therapy, we repeat the smear and if the finding is confirmed we proceed with diagnostic investigations that may include dilatation and curettage and cervical biopsy. When histologic evidence of the disease is found, we proceed with the definitive treatment of the recurrence.

Stage I and II cases, in particular, may benefit from the use of vaginal cytology for persistent or recurrent tumors; this should favor the treatment of these tumor manifestations when a better chance of success exists.

SUMMARY

1. A study of the prognostic significance of persistent tumor cells in the vaginal smear during the first postirradiation year in 342 patients with carcinoma of the uterine cervix is presented.

2. The number of negative and positive smears at 1, 2, 4, 6, and 12 months post irradiation is analyzed and a correlation is made with the tumor-free survival at 3, 4, and 5 years.

3. Persistent tumor cells in the vaginal smear have no prognostic significance when present before the 4th month post irradiation.

4. The absence of tumor cells in the smear taken 4 months or later after therapy is associated with a relatively good prognosis, particularly in Stage I and II.

5. The presence of tumor cells 4 months or later after therapy is associated with a poor prognosis.

6. An occasional patient may have tumor cells present in the vaginal smear as long as 12 months after treatment and never show further evidence of disease.

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BIOLOGIC BASIS OF PREOPERATIVE RADIATION TREATMENT*

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IT IS from an evaluation of the patients who fail to be cured of their cancer that we may look for the means and mechanisms to modify treatment and improve clinical care. Unfortunately, we have a very large patient material upon which we may make our investigation. The American Cancer Society estimates that "approximately 300,000 persons will die of cancer this year—approximately 800 per day, 1 every 2 minutes."[5]

Reports of clinical cure rate for selected head and neck tumors or for carcinoma of the cervix indicate an improvement in cure by a factor of 2 in the past decades.[12] These improvements in cure have come from early case finding and better patient care. However, in the recent past, there has been no significant variation in the cure rate in a number of other lesions, for example: carcinoma of the breast, colon or lung—the tumors causing the most deaths due to cancer.[5] Of this group, carcinoma of the lung may be considered a special case, as the increased frequency of occurrence, the relatively specific etiology (cigarette smoking) and the very low cure rate all suggest that this problem is probably best solved by prevention rather than cure. Carcinoma of the colon and carcinoma of the breast have been treated by radical and supraradical surgical and radiation therapy efforts with the only apparent improvement over the past three decades being that benefit associated with improved case selection but with no improvement in the over-all survival rate.[7,27]

It is the concern of clinicians responsible for the care of patients with cancer to develop improved methods of treatment—increased cure rate with decreased complication rate. To this end, any rational and well conceived modification of our therapeutic attack should be considered and evaluated. The addition of radiation therapy prior to the surgical resection of the lesion constitutes a conceptual change that can be tested and evaluated.

The major intent of the authors is to recommend a study in patients, and to this purpose, an attempt will be made to construct a rational basis for the use of preoperative radiation therapy to increase the cure rate of cancer, to suggest a mechanism by which irradiation might lead to benefit without undue increase in complications and to support by experimental evidence the validity and applicability of these theoretic considerations.

I. THEORETIC BASIS OF PREOPERATIVE IRRADIATION

A. PATIENTS WHOSE OUTCOME CAN BE MODIFIED BY PREOPERATIVE IRRADIATION

It is apparent from a study of the patients who fail after treatment that the failures occur by a number of processes.[24,38] It is necessary, first, to define those processes of failure that *can* be modified by preoperative irradiation and to separate these mechanisms of failure from those in which preoperative irradiation administered locally *can not* presently (with our present knowledge) increase the clinical cure rate. The methods of failure that *can* be modified include the following:

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1. *Local recurrence*: when in the case of irradiation or surgical extirpation of a tumor, a local recrudescence appears in the wound or at the margin of the irradiated field; tumor cells have been left unaffected in the patient and the cells left are sufficient in number and nature to reinitiate the tumor. In the case of the radiation therapy patient, a failure may be due to the radioresistance of an anoxic population of cells or due to cells outside the irradiated field (geographic miss). In the case of failure following local surgery, the recurrence represents regrowth of remnant cells from either tumor extensions which have been cut across at the time of surgery or from cells deposited in the wound at the surgical procedure (Fig. 1). The idea of tumor regrowth occurring from these remnant cells is not meant as an attack on the concept of surgical removal of tumor, but rather as a search for understanding of tumor recrudescence and for methods to reduce the recurrence rate.

2. *Tumor cell dissemination during surgery*. It is necessary to recognize that tumor cells can be disseminated at the time of the surgical procedure. Washings of the wound area and collections of blood from vessels draining the operated region have demonstrated the presence of tumor cells.[2,6,35–37] The finding of tumor cells at the site of a suture anastomosis performed at some distance from the original tumor, or the findings of tumor growing in graft donor site are all evidence for cell transplant at the surgical procedure (Fig. 1).[6] These phenomena occur as a result of the cellular nature of the tumor and the failures originating from these mechanisms suggest that a relatively small number of cells are able to initiate a tumor when the cells are in an adequate supporting environment. The fact that not all of the patients who have had demonstration of cell dissemination later developed metastases suggests that there are defense mechanisms to inactivate these cells or that a large number of cells or suitable lodgment of the cells is necessary for tumor regrowth and treatment failure.[6]

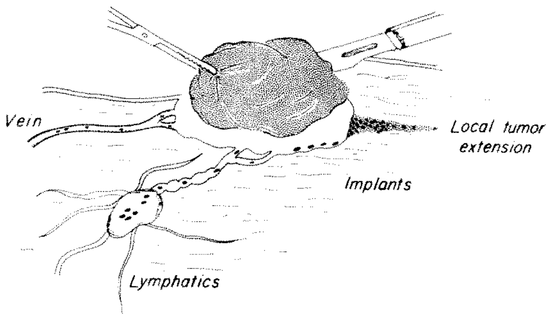


Fig. 1. Preoperative irradiation may be of value under the depicted conditions: tumor cut across; tumor cells implanted; lymphatic dissemination; vascular dissemination. (Modified from Cole, W. H. *et al.*[6] Appleton-Century-Crofts, Inc., New York, 1961.)

It is agreed that tumors most frequently fail because of cell dissemination due to entirely natural processes that take place prior to the first visit of the patient to a physician. Since as yet we have no effective answer to this early dissemination, it is only in those patients in whom tumor cell dissemination occurs at the time of surgery that we are able to postulate a difference in outcome by the addition of radiation administered preoperatively.

3. *Far advanced tumor*. Preoperative irradiation might be of value in those patients in whom the tumor is in immediate proximity to or infiltrating a structure vital to life or function. A suitable reduction in the size and extent of the tumor or inactivation of the tumor extensions into the vital organs may render an inoperable patient operable. Similarly, in the case where a tumor is in immediate proximity to structures that may be extremely radiosensitive, the use of a less than dangerous dose of radiation preoperatively may be rational.

B. PATIENTS WHOSE OUTCOME IS NOT MODIFIED BY PREOPERATIVE IRRADIATION

It is also necessary to define those other situations in which—no matter what the dose, no matter what the time period of administration, and no matter what the time period of waiting between irradiation and surgery—preoperative radiation ther-

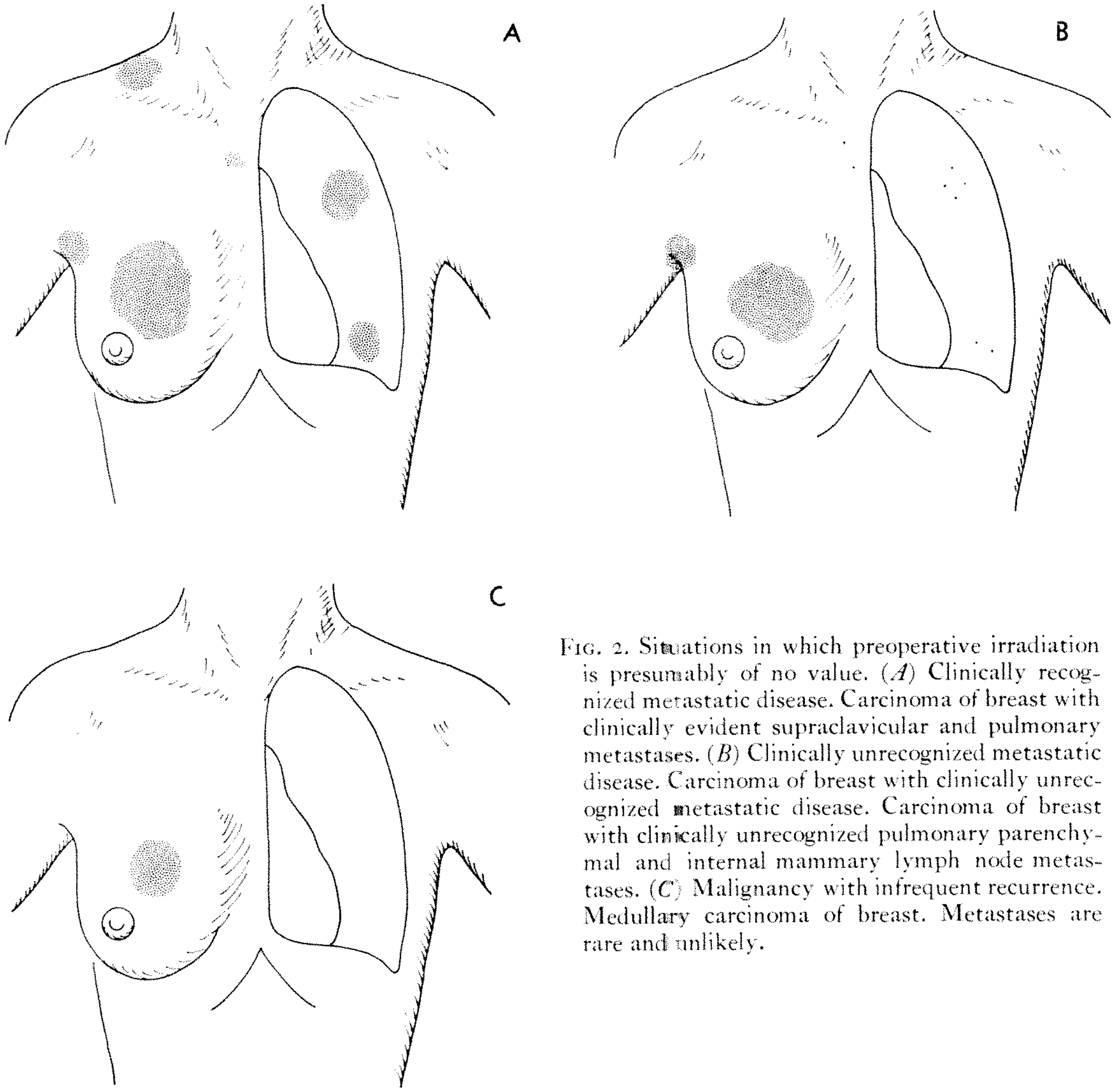


Fig. 2. Situations in which preoperative irradiation is presumably of no value. (*A*) Clinically recognized metastatic disease. Carcinoma of breast with clinically evident supraclavicular and pulmonary metastases. (*B*) Clinically unrecognized metastatic disease. Carcinoma of breast with clinically unrecognized metastatic disease. Carcinoma of breast with clinically unrecognized pulmonary parenchymal and internal mammary lymph node metastases. (*C*) Malignancy with infrequent recurrence. Medullary carcinoma of breast. Metastases are rare and unlikely.

apy cannot produce benefit. These cases and situations include the following:

1. *Patients with metastases*

a. *Clinically evident metastases.* In patients who have metastatic disease prior to the consideration for surgical therapy, no benefit can be obtained from the administration of preoperative irradiation. These cases include those who have clinically evident metastatic disease or wide local extension, which preclude any thought of curative surgery. Unless the preoperative irradiation affects the tumor metastases, cure will not be obtained. In these cases, since a curative surgical approach is unlikely, the lack of success will not be attributed to the failure of preoperative radiation therapy, but rather to the existing extent of the disease (Fig. 2*A*).

b. *Clinically unrecognized metastases.* Another group of patients may have clinically unrecognized metastases at the time of treatment (Fig. 2*B*). These are patients in whom metastases arise from cells disseminated at any time prior to treatment—whether by natural mechanisms, tumor manipulation, or biopsy procedures. The fact that these patients are not recognized and their frequency is not known makes it

impossible to eliminate them from any study series of cases. It must be recognized, however, that this group of patients (those in whom dissemination has occurred and metastases are present but unrecognized at the first visit of the patient to the physician) makes up the major population of patients who fail following treatment of cancer performed for cure. The high frequency of occurrence of this phenomenon—clinically unrecognized disseminated tumor—makes it unreasonable to expect a miraculous increase in cure rate by any new local therapy that we administer. Thus, because of this too frequent problem, preoperative radiation therapy can have only a limited benefit. It is also important to observe that an extremely large series of patients will be necessary in order to include a population of patients in which the treatment method may display its effectiveness. The group of patients with clinically unrecognized disease in which either of the alternative methods of therapy—surgery alone or preoperative irradiation plus surgery—is doomed to failure, dilute any random allocation series, and conceal benefits which may be produced in the patients whose outcome is modified.[3]

2. *Nonrecurring carcinoma*

A second large group of patients who will receive no benefits from preoperative irradiation are those individuals who have a tumor of such nature that cure is usual and failure to cure rare (Fig. 2*C*). Examples are lesions such as small carcinomas of the skin, selected histologic types of breast carcinoma, early stage carcinoma of the cervix, or histologically benign tumors which are life-threatening because of their location. If failure to cure is rare, only a small increment in cure can be expected, and it seems unreasonable to subject these patients to any risk associated with preoperative radiation therapy. This group of patients also would be detrimental to any study group, as the outcome can not be modified by the alternatives of treatment method, and therefore, this group also tends to dilute and hide any benefit that might be obtained.[3]

C. CHARACTERISTICS OF PATIENTS WHO WILL RECEIVE BENEFITS

From these considerations, it is possible to define the characteristic of the population of patients who will benefit from preoperative irradiation. These characteristics are:[28,29]

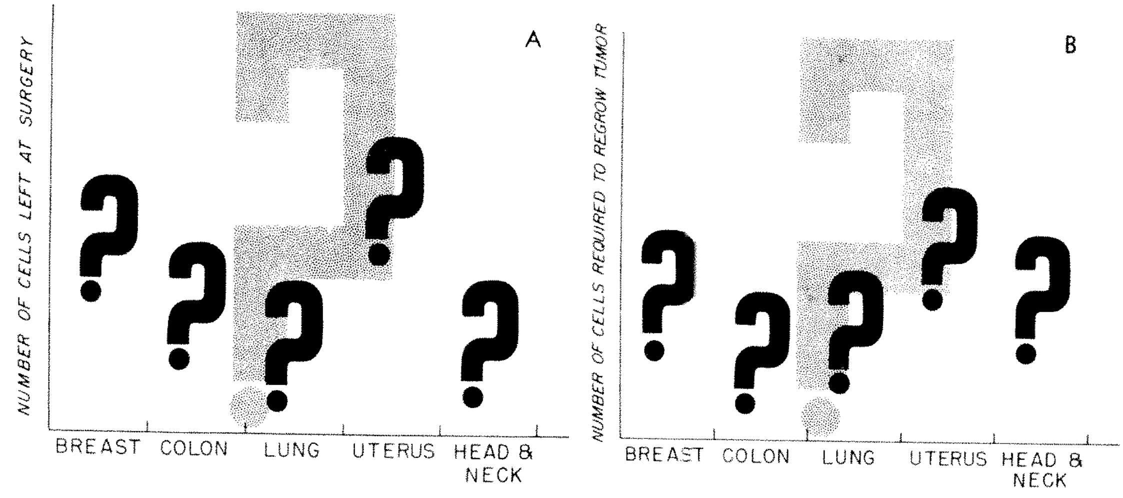
1. Viable cells capable of reinitiation of the tumor are left in the patient at the time of completion of either surgery or irradiation applied for cure.
2. The cells are included in the preoperative irradiation field.
3. The dose of preoperative irradiation administered must be such as to modify in some way the tumor cells that are left and thus prevent their regrowth as either metastasis or local recurrence.

D. MECHANISM OF RADIATION ACTION

It is apparent that irradiation can act by a number of mechanisms to produce the cell inactivation necessary for benefit. Those mechanisms that have been postulated include the following:

1. Either effects on the host that prevent tumor cells from growing into tumors, or
2. Direct effects on the tumor cells.

Among the host effects which have been postulated or described are fibrous encapsulation of cells or blockage of vessels or lymphatics, which trap tumor cells and prevent regrowth. Another possibility of the host effect is that "*immunity*" destroys tumor cells left locally or disseminated. Each of these mechanisms may exist and all are subject for experimental investigation as to the extent of their participation in the benefit of preoperative radiation therapy. Alternatively, it has been suggested that the primary effect of value in preoperative irradiation is the direct effect of ionizing radiation on the tumor cells. It has long been known that the primary effect of



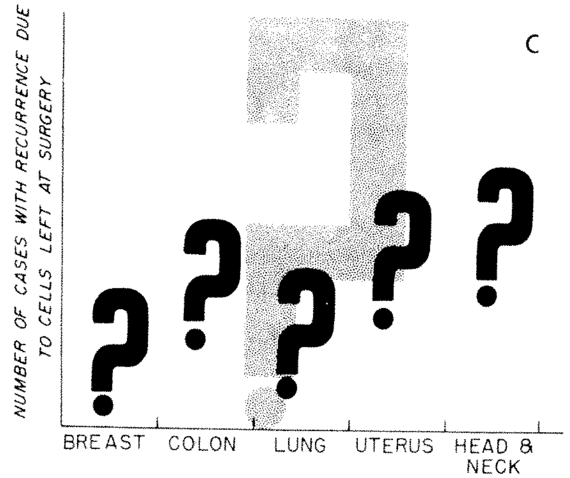


Fig. 3. The detailed mechanisms of postoperative tumor recurrence are unclear. (*A*) The number of cells left at surgery is not known. (*B*) The number of cells required to regrow a tumor is not known. (*C*) The number of cases in which recurrence is due only to cells disseminated or left locally at the time of surgery is not known.

radiation is destructive to the cells. Ever since this was recognized, it has been reasonable to perform localized preoperative radiation therapy as a means of destroying *in situ* tumor cells before operating. The particular relationship observed in radiation cell survival studies makes local preoperative radiation therapy an attractive adjuvant.[28,29]

E. CLINICAL PROBLEM

It is clear from observation of patients that there are several considerations that need be evaluated. We do not know the number of viable cells left in the patient at the time of the surgical procedure or local irradiation (Fig. 3*A*). If the surgeon is aware that he cuts across tumor or the radiation therapist aware that he is missing tumor cells, he modifies his procedure so as to encompass these cells. We do not know the number of cells required to initiate regrowth of the tumor in the patient (Fig. 3*B*). We know that the number is probably more than a single cell, but we have no significant measure as to how great a number it is. We are also quite unaware as to the number of patients in whom the failure is due to cells left or disseminated at the time of surgery (Fig. 3*C*). Thus, we can only guess at the size of the population of patients in whom a modification in cure can be produced by preoperative radiation therapy.

Ethical considerations preclude the performance in human patients of the biologic studies that will allow us to determine the radiation sensitivity of the tumor cells. We

are not allowed, nor is it reasonable to suppose that we ever should be allowed, to leave cells in patients in order to determine the number that causes a tumor. We must put our best efforts to improve the cure of each patient, rather than use him as a study system to obtain biologic knowledge.

II. ANIMAL STUDIES

From these considerations, it seems reasonable to attempt to simulate in animals a tumor cure model system and try to evaluate the basic mechanisms that contribute to preoperative radiation therapy benefit, and also to perform direct preclinical experiments studying the benefit of radiation administered preoperatively.

We are not able to determine (except indirectly) the number of cells left in the animal at the time of the surgical procedure. We have attempted to study the several phenomena available:

1. The number of cells necessary to cause a tumor in an animal.
2. The radiation sensitivity of these tumor cells.
3. The benefit of irradiation administered preoperatively.

The tumor system used in these experiments is the 6C3HED tumor (Gardner's lymphosarcoma) grown in young adult female C3H/anf mice. The mice are purchased from Cumberland View Farms, Clinton, Tennessee, and the tumors used in the experiments have come from a number of sources, including the Jackson Laboratories, Bar Harbor, Maine, and Dr. Robert F. Kallman, Stanford University, Palo Alto. The techniques of the cellular assay system, the random allocation procedure and radiation therapy procedures have been described.[28,29]

A. NUMBER OF CELLS TO CAUSE A TUMOR

In our studies, the number of cells required to initiate a tumor when the cells are transplanted into a new host, depends upon the characteristics of the host. It is apparent from Figure 4 that in the case of an

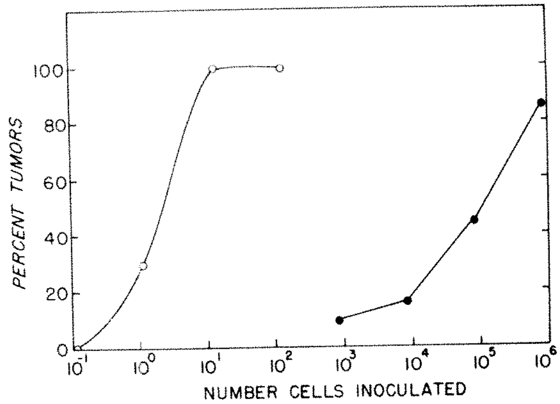


FIG. 4. The number of cells required to cause a tumor (6C3HED).

Open circles: Response of normal mice which have never been exposed to tumor cells. One cell causes 30 per cent of animals to develop tumors; 10 cells cause tumor to grow in 100 per cent of mice. *Solid circles:* Response of mice which have been cured of tumor. About 200,000 cells are required to cause tumors in 50 per cent of the animals. Tumor bearing mice require between 1 and 200,000 cells to cause growth of a new tumor.

animal which has never been exposed to the tumor cells, a very small number of cells is adequate to initiate tumors in the animals. On the other hand, in animals who have been cured of a tumor, a much larger number of cells is required. From other observations it appears that an animal in whom tumor is growing represents a case which is somewhat between the two extremes. This is probably reasonably similar to the clinical situation in which one cell (the theoretically minimum that could be effective) is not sufficient, and a very large mass (a gram or more) is not required.

B. RADIATION SENSITIVITY OF TUMOR CELLS

A study of the radiation sensitivity of this population of cells demonstrates similarity to the other *in vivo* and *in vitro* quantitative assays of cell survival that have been reported. Our results indicate a multicomponent survival curve in which the relation between the dose of radiation applied and the number of cells surviving represents essentially an exponential function (Fig. 5).[4,9,17–19,30,31,33,40,43]

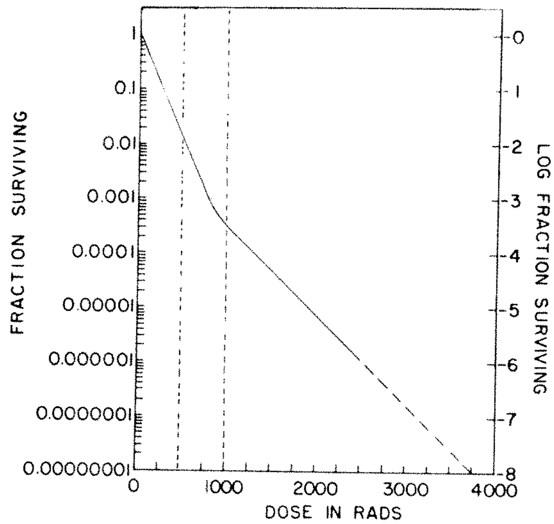


Fig. 5. Relation between dose of radiation and tumor-forming capacity of 6C3HED (Gardner lymphosarcoma) cells irradiated and assayed *in vivo* (1,800 mice).

It is clear that a small dose (500–1,000 rads, vertical lines) inactivates (kills) the overwhelming proportion of cells. A large dose (3,000–4,000 rads) is required to cure the tumor.

In other populations studied, there is variance in sensitivity of only about 4; this is sufficient to produce extreme differences in the fraction surviving a given dose of irradiation. In these studies, it is the survival of a cell (ability to continue to proliferate and reproduce indefinitely) which is being evaluated. In this sense, a cellular population is *sterilized*, *killed* or *inactivated* when the cell's capacity to proliferate and replicate indefinitely is destroyed. It is this particular biologic characteristic of a tumor cell which contributes to the tumor mass and to the death of the patient, and it is this particular characteristic of a tumor cell which must be destroyed if we desire to prevent a single cell or a small number of cells to initiate a recrudescence.

C. SIGNIFICANCE OF CELL SENSITIVITY STUDIES

The following general characteristics are observed in cell survival studies that have been performed *in vivo* and *in vitro* in normal cells and tumor cells, in animal cell studies and in human cells in tissue culture.[4,9,17–19,30,31,33,40,43] In the relationship between the dose of radiation and the surviving fraction, there has generally been observed a shoulder (which may or may not be present) followed by an essentially exponential relationship between the surviving fraction of cells and the dose of radiation applied. Some general implications and extrapolations from these data are of considerable importance to an understanding at a biologic level of some radiation effects as they may apply to clinical practice.

1. *All cells studied are radiosensitive.* The inactivation of cells appears to be a random process and the survival of a cell a probability function. Although the slopes of the exponential inactivation curves are different, all of the populations demonstrate a similar type response as regards cell killing. From this, it is possible to extrapolate that:

a. A small dose of radiation (500 to 1,000 rads) inactivates the major portion of the population of cells.

b. A very large dose of radiation (2,000 to 6,000 rads) will be required for inactivation of a sufficient proportion of cells as to cause a high probability of cure.

c. The proportion of cells inactivated with each increment of dose is similar on the straight line portion of the survival curve. This indicates that each additional given dose of radiation, while it inactivates the same proportion of cells, is progressively affecting a smaller total number of cells. This results from the fact that a smaller number of cells remains active and thus capable of being inactivated.

d. From the observation of biologic assays, it is apparent that the effect of radiation on cells is immediate. This does not in any sense imply that the changes resultant from this effect or the response of the cells to the radiation are going to be immediately expressed. As a matter of fact, the his-

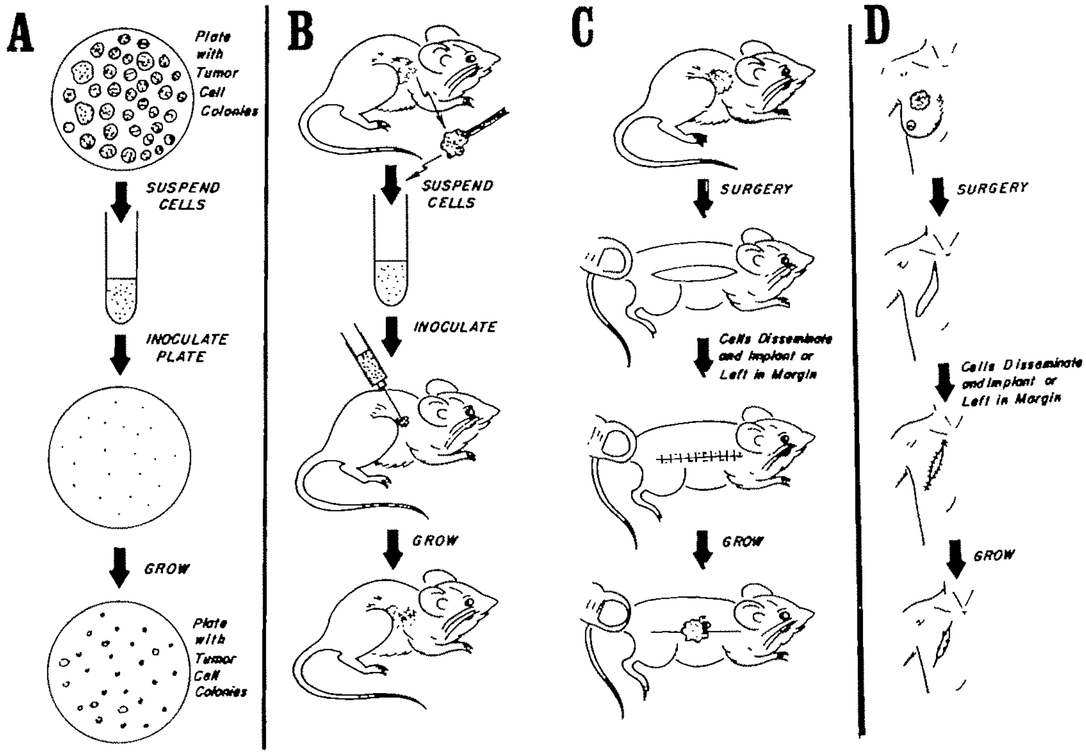


Fig. 6. Analogy between surgical failure and experimental tumor cell growth.
An analogy is presented suggesting that dissemination of cells at surgery (*C* and *D*) is equivalent to inoculation of cells in causing recurrences (*A* and *B*). In *A* and *B* it can be demonstrated that administration of small doses of radiation prior to inoculation causes a marked reduction in the capability of the cells to grow tumors (see Fig. 5).

tologic, cytologic and genetic consequences of the radiation may be masked for some period of time[42] and it may be necessary for cell division or other biologic stress or change to take place before expression of the damage.

As has been pointed out, nearly all of the cells studied have similar sensitivities within a relatively narrow range.[43] The similar sensitivity is indicated by the fact that the variation in slope of the exponential inactivation curves is only about a factor of 4.[43] It is also apparent from these curves, however, that this is sufficient variation to explain the tremendous variation in sensitivity of tumors in patients that we treat.

It is clear from observation and extrapolation from experimental evidence that there is nearly as much variation in the sensitivity of a population of cells due to the condition and environment of cells at the time of irradiation as there is variation of the cell type.

It is apparent from studies[8] that fractionated radiation therapy has a considerably different effect than single doses, due to the demonstrated cell recovery in the interval between fraction of radiation.

D. PREOPERATIVE IRRADIATION ANALOGY

Since we are not able to perform cell survival studies and biologic investigations in man, it seems reasonable to consider how far a proposed analogy will apply in a preclinical study and estimate the usefulness of this analogy to the clinical problem (Fig. 6, *A-D*). To this end, we have set up an analogy between a tissue culture plate of tumor cells and an animal with a tumor. In each case, cells removed from the original

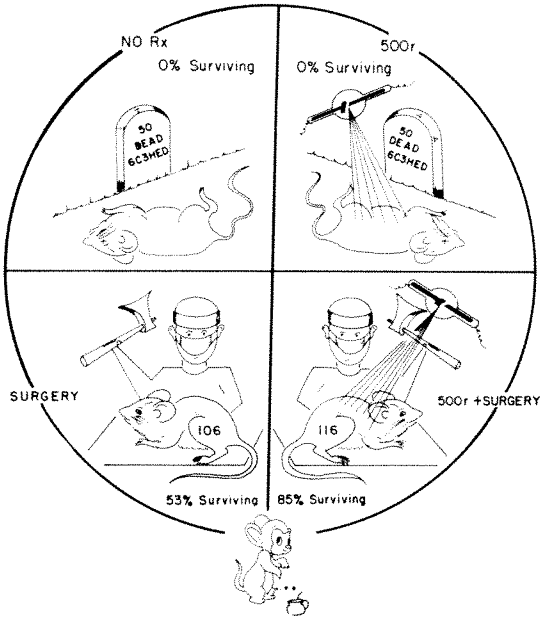


Fig. 7. Animal experiment to test the value of preoperative irradiation.

No treatment—all animals died of tumor.

500 rads to tumor—all animals died of tumor.

Surgery*—53 per cent survived, tumor-free for 200 days.

500 rads to tumor+immediate surgery*—85 per cent survived, tumor-free, for 200 days.

Statistically significant: P=0.001.

* Surgeon did not know which mice had been given roentgen-ray treatment and which had not.

suspension or tumor and then inoculated into either an animal or another culture plate will result in tumor cell growth to form a colony or a new tumor (Fig. 6, *A* and *B*). In each of these instances, the tumor cell has manifested its capacity to continue to divide. We know from experiments[4,9,17–19,30,31,33,40,42] that irradiation performed at any time changes considerably the probability that cells will grow to a colony in the plate or into a tumor in the animal. We can also observe in the animal system that if we remove the tumor surgically and tumor cells are left, tumors will regrow (Fig. 6*C*). In clinical practice, we observe instances in which a patient with cancer has a surgical procedure and tumor cells left in the wound grow into a recurrence of the tumor (Fig. 6*D*). It can be argued, therefore, that since radiation in relatively small doses is effective in reducing tumor recurrence in the first two instances, it should be effective in the last two as well. If irradiation proves beneficial in the preclinical study, it seems reasonable to perform a similar study in man. For this reason, it was desired to test the hypothesis that *If a dose of radiation less than that required for cure is administered it significantly modifies the surgical cure of a tumor*, by studying an animal tumor system.

E. PREOPERATIVE IRRADIATION IN ANIMALS WITH TUMORS

This study was performed in a population of animals in which tumor was transplanted and allowed to grow subcutaneously. The animals were then randomly allocated into separate treatment groups. The tumors were either irradiated or not irradiated, and the mice operated upon immediately. The surgeon was not informed as to whether the animals had received radiation and consistently performed the best operation to remove the tumor. The experiment and the results are indicated in Figure 7. It can be demonstrated that in animals in whom no radiation therapy had been applied, all of the 50 animals died. Similarly, in the 50 animals who received 500 r to the tumor area, all of the animals died of tumor. In a similar population, animals had the surgical procedure performed; 53 per cent of the 106 animals operated survived for over 6 months without evidence of tumor recurrence. In another parallel group of 116 animals in which 500 r was given preoperatively and the surgeon immediately resected the tumor (the surgeon not knowing that the group had preoperative radiation therapy), there was a significant improvement, with 85 per cent surviving free of tumor recurrence. The probability of this occurring due to chance (χ^2 test) is $P<.001$. Similar studies have been performed on other animal tumor systems (Table 1). In these it appeared that a relatively low dose of radiation (less than a curative dose)

Table I

SUMMARY OF MOUSE PREOPERATIVE IRRADIATION DATA

Tumor	Approx. dose of irradiation to cure 50%	Survival with surgery alone		Preoperative irradiation dose	Survival with preoperative irradiation and surgery	
B16-Melanoma	5,000 r	75/122	62%	1,000 r	94/115	82%
KHT	5,000 r	33/51	65%	1,000 r	33/53	62%
		47/72	62%	1,000 r	41/65	62%
		52/76	68%	3,000 r	56/80	70%
KHAA	5,000 r	18/60	30%	1,000 r	40/60	66%
		19/57	33%	2,000 r	37/46	80%
		10/36	27%	2,000 r	21/28	75%
		6/61	10%	3,000 r	29/66	44%
KHDD	5,000 r	29/63	46%	1,000 r	45/67	67%
BW 10232	5,000 r	110/133	82%	1,000 r	103/129	80%
KHSH	5,000 r	31/31	100%	1,000 r	27/27	100%
6C3HED	1,700 r	56/106	53%	500 r	99/116	85%
6C3HED (imm inc)*	3,200 r	1/75	1%	500 r	15/75	20%
6C3HED (imm inc)*	3,200 r	0/20	1%	1,000 r	10/20	50%

* imm inc—rendered "immunologically incompetent" with 250 rad whole body dose and cortisone before tumor inoculated.

B16-Melanoma—significant benefit at $\frac{1}{5}$ curative dose

KHT—no benefit in 3 experiments with doses up to $\frac{3}{5}$ curative dose

KHAA—significant benefit at $\frac{1}{5}$ curative dose. Increased benefit with larger dose ($\frac{2}{5}$ curative) in 2 experiments. With very large, nearly inoperable tumors, a dose of 3,000 rads produced significant benefit

KHDD—significant benefit at $\frac{1}{5}$ curative dose

BW 10232—no benefit

KHSH—no benefit; 100 per cent cures with or without irradiation

6C3HED—significant benefit at $\frac{1}{3}$ curative dose

6C3HED (immunologically incompetent)—significant benefit, with increased benefit at higher doses

significantly modified the curability of the tumors in almost all of the tumors. The discrepancy from the hypothesized results is pointed out in the caption.

In all of the experiments the surgical wounds healed completely although often delayed.

F. WOUND HEALING

The question must be raised, "How can a surgical wound heal if the normal cells are equally sensitive to the radiation doses as the tumor cells?" While the mechanism of healing is not clearly known, it is possible to speculate that wound healing occurs primarily from cells that have grown into the wound area from other unirradiated parts of the body—certainly such is the mechanism of healing of radiation epidermitis produced in the normal skin during the curative treatment of skin cancer. In any case, while the mechanisms of wound healing are not clear, the wound healing complication rate should not be excessive following discreetly applied preoperative radiation therapy.

To this end, a series of experiments has been performed in animals to determine the interference to wound healing by preoperative irradiation. In these studies, a group of animals was divided by random selection into similar smaller groups, each to be treated differently. The common treatment was a surgical procedure consisting of excision of an ellipse of skin followed by suture of the wound. The various groups of mice received graded doses of roentgen rays to a larger ellipse of skin including the entire area of the proposed surgical wound. The surgeon was not aware of the dose of radiation that had been applied, but performed similar duplicate operations. All mice were examined daily to determine wound healing. There is observed progressive increase in wound healing delay with increasing dose of radiation (Fig. 8).

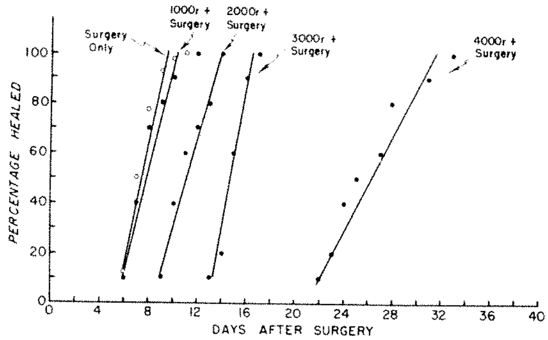


Fig. 8. Relation between wound-healing delay and dose of roentgen rays to skin.

Forty mice used to construct each curve. Mice were irradiated, an elliptic piece of skin removed, and the wound sutured. Surgeon did not know which mice had received radiation and which had not.

1,000 rads—no delay.
2,000 rads—slight delay.
3,000 rads—moderate delay.
4,000 rads—very marked delay.

III. DISCUSSION

A. ALTERNATIVES TO PREOPERATIVE IRRADIATION

It is apparent that there are other alternatives to the use of preoperative irradiation to control cells left or disseminated at surgery.

1. *Drug therapy.* It is reasonable to consider the use of drugs or chemicals which are destructive to cells. While cytotoxic drugs would seem useful preoperatively, their successful employment, if administered systemically, requires differential action, specifically inactivating tumor cells in preference to normal cells; and if administered locally, requires that the drugs reach and affect all of the tumor cells. These conditions do not appear to be fulfilled.

2. *Postoperative irradiation.* As another alternative to preoperative radiation therapy, it is reasonable to consider the use of postoperative irradiation. In this circumstance, it is possible to speculate on the variation in benefit to be obtained as contrasted to that from preoperative radiation therapy. Irradiation given postoperatively would not be injurious to cells that had been distributed outside the wound area at the time of the surgery. Since no irradiation precedes surgery, cells disseminated systemically by either lymphatic or vascular routes or cells transplanted to a distant site at the time of surgery would not be affected. It appears that postoperative radiation therapy would not succeed in such patients. In the alternate situation, that of cells left in the operative site, it is probable that these cells would be affected equally by postoperative treatment as by preoperative. Such equivalent result, however, requires that these cells be at the same radiation sensitivity as they would have been at the time of initial preoperative radiation therapy. Since it is possible that the cells that are either shed or cut across in the operative procedure are peripheral, relatively well growing cells, it is possible that these cells will be more sensitive than those left in the operative wound in which region the oxygen tension may be reduced. If there is sufficient modification of the oxygenation of these cells by the operative procedure so that the cells are relatively unoxygenated in the postoperative period, their radiation sensitivity may be considerably altered.[15,18] Another consideration which is detrimental to the use of postoperative radiation therapy is that the irradiation is applied to those cells involved in healing the surgical wound. If these considerations are valid, it seems that preoperative radiation therapy has a greater probability of benefit than the use of preoperative drugs or postoperative radiation therapy.

B. OPTIMAL PREOPERATIVE IRRADIATION

It is not adequate to presume that preoperative radiation therapy is of benefit (Table II).[1,10,11,20–22] It is necessary to consider how beneficial it is and how to optimize this benefit. It is apparent that we must evaluate several treatment characteristics, namely, the optimal dose, the optimal time over which this dose should be applied, and the optimal delay between irradiation and operation. We must observe

Table II

OTHER ANIMAL TUMOR PREOPERATIVE IRRADIATION DATA*

Author	Tumor	Approx. dose to cure 50%	Cure with surgery only	Preoperative irradiation dose	Cure with preoperative irradiation and surgery
Nakayama *et al.*[26] (1963)	MH134 Mouse hepatoma	Not stated	3/19 (16%)	2,000 r (2 days delay) for surgery)	5/18 (28%)
Agostino and Nickson[1] (1960)	Walker 256 Carcinosarcoma	Not stated	21/100 (21%)	800 r (1 day delay for surgery)	40/100 (40%)
Inch and McCredie[21] (1963)	Walker 256 Mammary carcinoma	6,000 r (90% cure dose)	18/35 (51%)	2,000 r	30/34 (88%)
Inch and McCredie[21] (1963)	C3H Mammary carcinoma	6,000 r (50% cure dose)	36/63 (57%)	2,000 r (1 day delay for surgery)	40/63 (66%)
Inch and McCredie (1964)	C3H Mammary carcinoma	6,000 r (90% cure dose)	33/84 (39%)	2,000 r (6 days delay for surgery)	42/71 (59%)

* Cell survival studies are not included in the table, but are listed in the bibliography

the effects not only on the tumor, but also on the healing mechanisms that will be necessary to preserve life and function.

1. *Optimal dose for a given time of administration.* The characteristics of the dose of radiation to be applied for greatest beneficial effect depend upon several factors:

a. The number of tumor cells left or disseminated at surgery.
b. The number of cells required to reinitiate a tumor.
c. The radiation sensitivity of the tumor cells.
d. The radiation sensitivity of the normal structures required for healing.

Tumor cells are spilled in the operative wound and the circulatory system, but as pointed out, the frequency of this occurrence and the number of cells remnant is not known. It is apparent that at least one cell is needed to cause recurrence, but it is possible that more are required. It is even possible that there will be a great variation in the number of cells needed, depending on the characteristics of agglomeration, distribution and environmental conditions at the site of deposition. We have inadequate information about these parameters, but it is probable that a large number of cells may be required, since it has been demonstrated that all patients who have circulating cells do not develop tumor recurrences.[6] If more than one cell is required to initiate a tumor, the probability of a recurrence depends on the ratio between the number of cells left in the patient and the number of cells required to regrow the tumor. If the ratio is one or more, the probability of recurrence is great. If the ratio is less than one, the probability of recurrence should be small. A third factor of significance is the radiation sensitivity of the tumor cells as they exist in the patient. In the reported *in vivo* and *in vitro* tumor cell studies, there is some difference in radiation sensitivity of the cells of various tumors studied as well as variation in sensitivity, depending upon the degree of oxygenation of the tumor cells. We have no way of knowing the oxygen tension or the radiation sensitivity of human tumor cells, and we are unable to determine what extrapolation from studies of animal tumor cells or human cell culture might be reasonable.

We are largely ignorant of the radiation sensitivity of the normal tissues, either normal cells or the supporting connective tissues. It is these cells that are required for healing the surgical wound produced at the excision of the tumor. It may even be that the healing takes place by migrating normal cells. This opportunity for migration of unchanged cells from unirradiated areas into the wound site is relatively unique for preoperative radiation therapy, which is one of the few forms of directed localized treatment to be administered preoperatively. In the case of postoperative radiation therapy, the healing cells are subject to the damage of the treatment. In the case of the systemic use of drugs in lieu of preoperative radiation therapy, the cells concerned with healing, even though they are at a distance from the wound, and would migrate into the wound to aid in healing, would also necessarily receive a toxic effect from the systemic agent. Of possible benefit is protracted and fractionated roentgen therapy administered preoperatively. It may be that the kinetics of cell turnover in the normal cells permit the type of repopulation that is observed in the therapy of pelvic carcinoma, in which the small bowel epithelium—one of the most rapidly growing in the human organism—is not destroyed or denuded in the course of curative dose administered to the tumor.

2. *Fractionation and time distribution.* Another factor that will modify considerably the optimal characteristics of preoperative radiation therapy will be the fractionation and the time period over which the treatment is applied. This fractionation may permit a repopulation of some of the normal tissues. Delay may, however, also be associated with an increase in radiation resistance of the tumor or repopulation of tumor cells. It is necessary to figure out which of these is going to be occurring to the greater extent so as to produce the best net benefit.

3. *Delay between irradiation and surgery.* Another consideration is the optimal delay between irradiation and the surgical procedure. A delay period may permit repopulation of the normal cells which would improve healing, but the delay may also be associated with a repopulation of tumor cells, which would be antagonistic to our goal. In some cases of very far advanced and extensive tumor, some delay must be utilized to permit shrinkage of the tumor as an expression of cellular radiation damage. In this case, it is reasonable to delay to permit regression of tumor from the sensitive structures, so that the patient may be operated upon with greater technical ease. The characteristics of the time delay are critical, as they may also be associated with a variation of wound healing. It is necessary, however, in any case to point out that we must suppose that there will be some increase in wound complications if we expect to increase the cure rate. In certain areas of the body, an interference with healing may be of limited concern to the patient; in others, an increase in complication rate or of the severity of the complications might be so damaging as to preclude the utilization of the preoperative radiation therapy.

C. SPECIMENS REMOVED AFTER PREOPERATIVE IRRADIATION

Evaluation of morphologic changes in the specimens observed after preoperative radiation therapy permits study of aspects of the response to irradiation of the tumor and the adjacent normal tissues which have been necessarily irradiated and removed with the tumor. It is possible to observe either of two phenomena, and it is necessary to make some modern-day interpretation of each of these.

1. *No tumor seen in specimen.* One of the phenomena concerns the situation in which no tumor cell is seen in the specimen, although a less than curative dose of radiation therapy had been administered.[25] To explain this, we must consider that even a careful examination of a considerable number of microsections is not adequate in the absolute sense to determine the presence or

absence of a few remaining tumor cells. Only a minute portion of the specimen is examined, and in this circumstance, if the distribution of the remaining viable cells is random, it is possible that a typical histologic appearance may not be in evidence and detection might be difficult.[34] It must be recognized, therefore, that the statement that no tumor cells are found is not proof that the tumor is, in fact, sterilized or cured. In the animal tumor systems, determination of the presence of reproductively viable cells is evaluated by a biologic test. Unfortunately, no such technique is available for evaluation of the surviving fraction ot the cells of a tumor in man. Only the clinical outcome of the therapy permits an evaluation of whether or not surviving cells are left.

2. *Tumor cells still present in specimen.* In the second case, where tumor cells are present and no radiation effects seem apparent, it must be recognized that the appearance of identifiable cytologically intact cells found in the resected specimen indicates only metabolic viability, as indicated by the staining quality. This observation does not determine or represent the reproductive capacity of the cells' future.[39] It has been observed that cells damaged sufficiently that death ensues may metabolize for some time and even undergo several divisions before dying.[39] Similarly, radiation damage may be long concealed if the cell is not called upon to divide. In this circumstance, the radiation damage may be masked until a functional test (division or reproduction) is applied.[42] Since it is the presence or absence of reproductively viable cells that is of ultimate concern to the recurrence of tumor, it is necessary that we be very careful not to make incorrect extrapolations from pathologic evidence.

3. *Changes in normal tissues.* Similar problems exist in the evaluation of normal tissue. It is difficult for the pathologist to evaluate specific changes due to radiation because there are apparently only characteristic vascular changes that are associated with high dose radiation therapy.[25] It is difficult to quantitate in a population of patients, each receiving similar dose, the frequency distribution of these vascular changes, and the early changes resulting from moderate doses of irradiation may be relatively nonspecific. Again, it is a functional test which we need to apply—wound healing or lack of healing—rather than the histologic test, which is of our ultimate concern.

D. TYPES OF PREOPERATIVE IRRADIATION

It is apparent from the foregoing that in cases in which only a small number of cells are left in the patient at the time of surgery, a different type of preoperative radiation therapy is applied, as contrasted to cases in which the tumor is extensive and possibly involving or impinging upon vital structures. In the former case, a relatively small dose of radiation with a small delay may be all that is required. In the latter case, it is necessary to consider a very large dose of radiation, probably approaching the curative dose. It is possible in the second case of the extensive tumors, to accept a high probability of complications and a moderately destructive series of procedures, as the alternative may be death due to controlled disease. Therefore, it behooves us to recall that we have a spectrum of considerations for preoperative radiation therapy, and that we should seek to apply treatment that is reasonable and proportional to the response needed—low doses with low complication rates in those cases where there is a probability of failure due to small population of cells disseminated, and high doses with the probability of significant increase of complication rate in those cases in which the cure is highly questionable.

E. TYPES OF OPERATIONS NEEDED

Similarly, we must recall that the operation that is to be performed must be carefully considered. In the case of the patient who received a very small dose of radiation, there may be only partial regres-

sion of the tumor, and certainly inactivation of only a portion of cells. Therefore, it seems reasonable that the operation must encompass all of the structures that would ordinarily have been removed, had preoperative radiation therapy not been applied. It is necessary to plan the surgical procedures in advance and clearly identify the size of the tumor and its probable extensions and the margins of the operative field, before radiation induced regression causes such a change as to make the tumor identification impossible. Alternatively, in the case of high dose radiation therapy, it is very possible, although this concept and experience are not so clearly defined, that the operation may be reduced in scope. It is probably a great error to unnecessarily reduce the scope of the operation in even these cases. Surgery should be very carefully planned prior to the institution of either portion of the therapy, and it is probable that any identifying means to demonstrate the probable preoperative extension and margins of the necessary operation is desirable. In our hands, we have used tattooing of the mucosal structures in order to define the extent of the operation planned prior to the treatment and resultant modification of the tumor landmarks. This is necessitated by the fact that there is often such a complete regression of the tumor that the surgeon is unable to define the area where the tumor existed, and is hard-pressed to define, therefore, the area that should be resected and the limits and margins of this resection. In the case of the advanced tumor, it is not so difficult; the surgeon removes that which is possible and leaves those structures which are necessary to preserve function. It seems that a rational approach in a clinical situation can be obtained.

F. NEED FOR PRECLINICAL STUDIES IN ANIMALS

It is apparent that no patient series is or can be large enough to permit evaluation of all of the parameters and characteristics possible to use in preoperative radiation therapy as the number of unknowns permit such a number of permutations as to preclude clinical evaluation of all of these

Table III

SIGNIFICANT CLINICAL STUDIES EVALUATING THE BENEFIT OF PREOPERATIVE IRRADIATION

Author	Tumor	Survival or recurrence free with surgery only	Dose preoperative irradiation	Survival or recurrence free with surgery following preoperative irradiation
Mallams *et al.*[23] (1964)	Bronchogenic carcinoma (superior sulcus)		3,000 r	8/24 (L&W) (33%) 2 years
Nakayama *et al.*[26] (1963)	Esophageal carcinoma	15/68 (22%) 3 years	2,000 r–3,000 r	20/44 (44%) 3 years
Leaming *et al.*[22] (1961)	Rectal carcinoma (Duke's C)	46/201 (23%) 5 years	800 r–1,200 r	72/195 (37%) 5 years
Henschke *et al.*[16] (1964)	Metastatic epidermoid carcinoma to neck lymph nodes	41/61 (67%)* 1 year	2,000 r	53/61 (87%)* 1 year
Fletcher *et al.*[13] (1964)	Advanced mammary carcinoma	60% (301)†	3,500 r–5,000 r	70% (254)†

* Recurrence free locally.

† Berkson-Gage.

combinations. It, therefore, seems reasonable and necessary to institute further studies of a preclinical nature in animal systems which stimulate the patient populations and problems. It is reasonable in these systems to study the characteristics and mechanisms associated with tumor dissemination and tumor cures, or with radiation sensitivity and wound healing problems. It is from these studies of mechanisms that we may be able to extrapolate by understanding the mechanisms as they take place in man, rather than by a dose or delay or other particular direct extrapolation to man.

G. NEED FOR CLINICAL STUDIES

It is similarly necessary that well controlled clinical studies be obtained in man in order to define the nature and extent of benefit of preoperative irradiation and preclude undisciplined utilization of preoperative irradiation as an habitual means rather than as a reasonable and educated directed effect. Fortunately a number of critical clinical studies are now underway. A number of clinical studies have been reported to show some benefit from preoperative irradiation (Table III).

SUMMARY

A biologic basis of preoperative radiation treatment has been presented and the various factors governing its application have been discussed in detail.

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A NEW AFTERLOADING TECHNIQUE FOR INTERSTITIAL IRRADIATION USING RADIOACTIVE MICROSPHERES*

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TWO principal methods are employed in the management of cancer by radiation; (1) irradiation from external sources, and (2) interstitial implantation of radioactive materials. External irradiation is easily administered; hence, it is most widely employed. Various techniques such as the use of multiple ports and wedge filters are used to help circumscribe the volume irradiated to high dose. Nonetheless, irradiation of normal tissues in the path of the beam cannot be avoided. It is often the amount of radiation that these normal structures will tolerate that limits the dose delivered to a particular site.

The introduction of radioactive materials directly into the part to be treated constricts the volume irradiated more effectively. Thus, high doses can be given to the tumor while all but the immediately adjacent normal tissues are spared. Interstitial implantation of radioactive materials is employed in either of two ways: (1) as a primary procedure, especially in cases of small tumors, or (2) as an adjunct to external irradiation preceding, during, or following its use.

Two kinds of implants are used commonly. The first is the removable implant where, typically, radium needles are removed after the specified dose has been delivered. The second is the permanent implant wherein radioactive sources of short half-life are left in place permanently. This latter technique is quick, better tolerated by patients, reduces discomfort, obviates the need for repeated instrumentation, and shortens the hospital stay. Permanent implants using conventional sources are applicable only to relatively small lesions.

There are some disadvantages in the traditional technique for interstitial implantation, especially those of the removable type. Long, rigid, radioactive sources are sometimes difficult to insert when limited space is available for insertion. They act as internal splints and may interfere with normal motility and function; for example, swallowing. Debilitated persons cannot tolerate the metallic appliances for any length of time and are particularly prone to develop infections at the implantation sites. Coupled with these limitations is the fact that the operator frequently receives a relatively high dose of radiation during the process of implantation and removal.

"Afterloading" techniques have been developed[4,7,11,12,15] so as to minimize the dose to the operator. Nonradioactive guides such as wires, needles or tubes are inserted in the desired arrangement. The operator is not exposed to radiation during this stage. When the position of the guides is considered satisfactory, the radioactive sources are introduced along predetermined paths.

Other methods have been devised to circumvent some of the problems listed above. One of these is the injection of colloidal suspensions of such radionuclides as Au^{198} and P^{32} directly into tumors.[5,6,10,13,14] However, the colloids migrate from the original needle tracks to a certain extent and accurate dose determinations are difficult. Normal structures outside the treatment volume thus are irradiated unnecessarily.

Finally, particulate radioactive material in the form of microspheres added a new weapon in the radiotherapeutic armamen-

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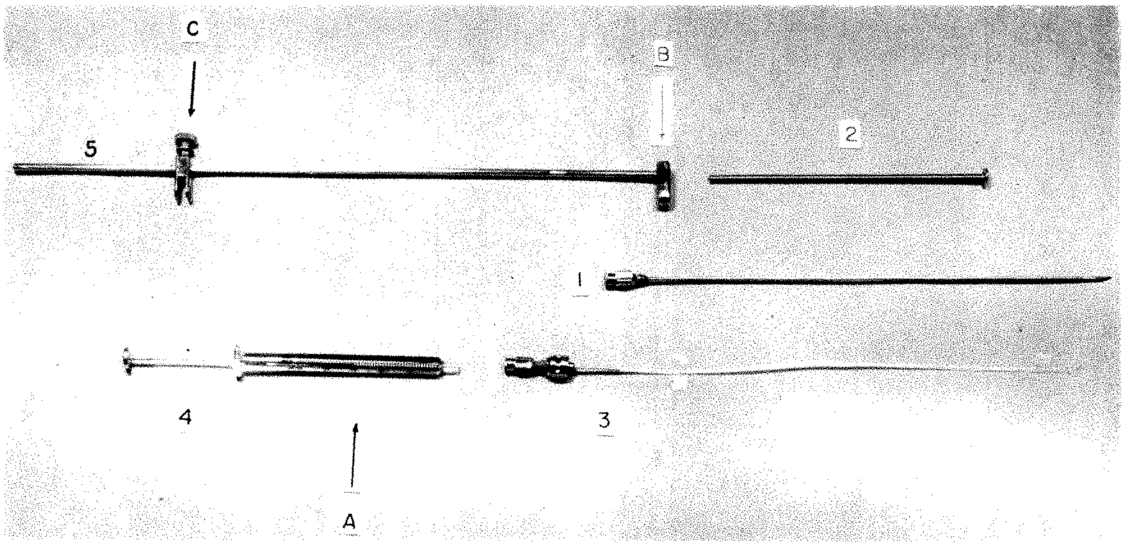

FIG. 1. Instruments employed: (1) stainless steel needle, 15 gauge; (2) flexible (helical) steel jacket; (3) teflon tube connected to double "Luer Loc" hub; (4) "microliter" syringe; and (5) rod with U-shaped end pieces B and C (C is adjustable).

tarium.[2,8,9,16] Techniques for the treatment of cancer by the intra-arterial instillation of these minute sources were soon developed, but rheologic considerations in large measure govern the deposition of the microspheres under these circumstances. Unpredictable inhomogeneities of the radiation dose patterns result,[16] and dose estimations are necessarily inaccurate.

These difficulties are not entirely solved by the methods described by Blanchard and his colleagues[3] or by Ariel,[1] who employ interstitial injection of the microspheres. Accuracy of placement, even distribution of the microspheres in predetermined quantities, and afterloading are all important if the desiderata of homogeneous irradiation of the affected part with minimal dose to the operator are to be attained. These criteria are not satisfied in the references quoted.

Success is assured if a known volume of the microsphere suspension with a known activity of the radionuclide selected is deposited with uniform linear activity along tracks of predetermined length with a specified distance between each track. Standard rules for the distribution of interstitial radioactive sources to achieve homogeneous irradiation of tissues such as those of Paterson and Parker can thus be followed. The technique here described was designed to incorporate these essentials.

MATERIALS AND METHODS

The "microspheres" incorporating the desired radionuclide have a diameter of about 15 microns, and are supplied in 10 per cent dextran solution.* Isotopes with low energy photons such as I^{131} and Yb^{169} are currently being employed since the dose to the part implanted is uniform with these isotopes while the integral dose to the adjoining normal tissues as well as the dose to the operator is low. The special instruments required are few in number and are easily fabricated (Fig. 1). The assembly of the instruments is shown in Figures 2 and 3. The microsphere suspension adequate to fill the desired length of track is entirely contained in the discardable teflon tube as it lies threaded inside the needle. The radionuclide is deposited interstitially as the syringe-needle assembly is withdrawn. The predetermined quantity of microsphere

* Such suspensions of microspheres with specified isotope, activity and volume are available from 3M Company, 2401 Hudson Road, St. Paul, Minnesota.

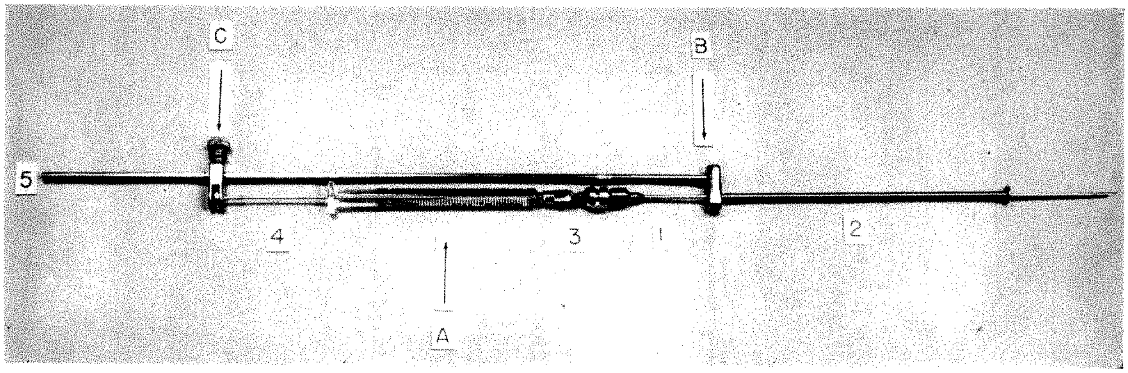

Fig. 2. Instruments assembled with straight stainless steel needle.

suspension of specified activity is evenly and totally deposited by the time the tip of each needle emerges. The steps followed when using this technique are as follows:

Preliminary plan and assessment of volume of microsphere suspension.

(1) The interstitial implant is planned according to the usual practice of the operator and the desired arrangement of the radioactive sources determined.

(2) Standard tables, such as those of Paterson and Parker, are consulted to determine the number of milligram hours of radium needed for the desired dose.

(3) The activity of radioactive microspheres required is then calculated as follows:

Total number of mc hr. of radionuclide through its decay = number of mg. hr. of

$$\text{Ra} \times \frac{\text{I gamma Ra}}{\text{I gamma radionuclide}} \times$$

filtration correction.

Total number of initial mc radionuclide =

$$\frac{\text{number of mg. hr. of Ra}}{\text{average life of radionuclide in hours}} \times \frac{\text{I gamma Ra}}{\text{I gamma radionuclide}}$$

$\times$ filtration correction.

(4) The volume of the radioactive microsphere suspension is derived as follows:

The number of tracks of injection are determined from the implantation rules. The length of each track is determined from the disposition of the tumor according to usual practice. The linear displacement of the plunger of the microsyringe when assembled (Fig. 2; and 3) is the same as the length of the track over which the radioactive microspheres are to be deposited.

The volume to be used in each track is predetermined in the following manner; the plunger of the microsyringe is withdrawn a distance equal to the length of the track to be implanted and the desired volume is then read directly from the graduations on the barrel of the microsyringe (Fig. 1, arrow A). From the total number of tracks the volume of microsphere suspension is easily determined. The above considerations enable one to precalculate all relevant specifications such as differential concentrations and volumes required for the belt, core and end tracks of a Paterson-Parker implant.

The implantation procedure is shown semidiagrammatically in Figure 4. The

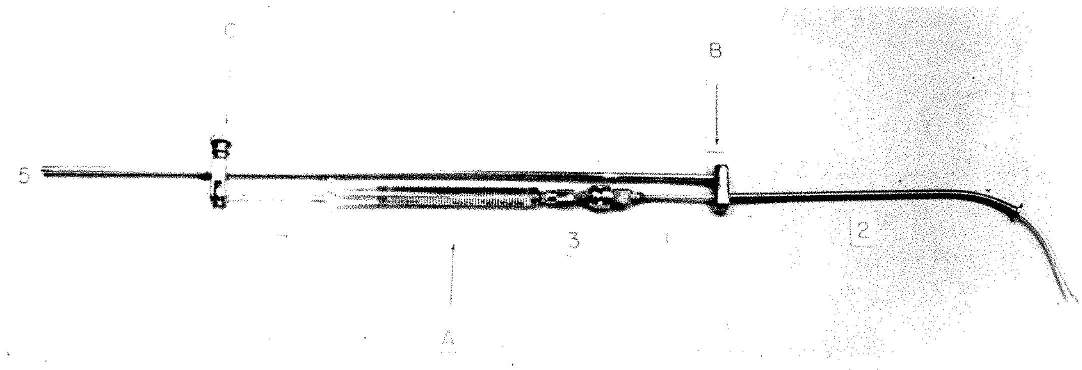

Fig. 3. Instruments assembled with curved stainless steel needle.

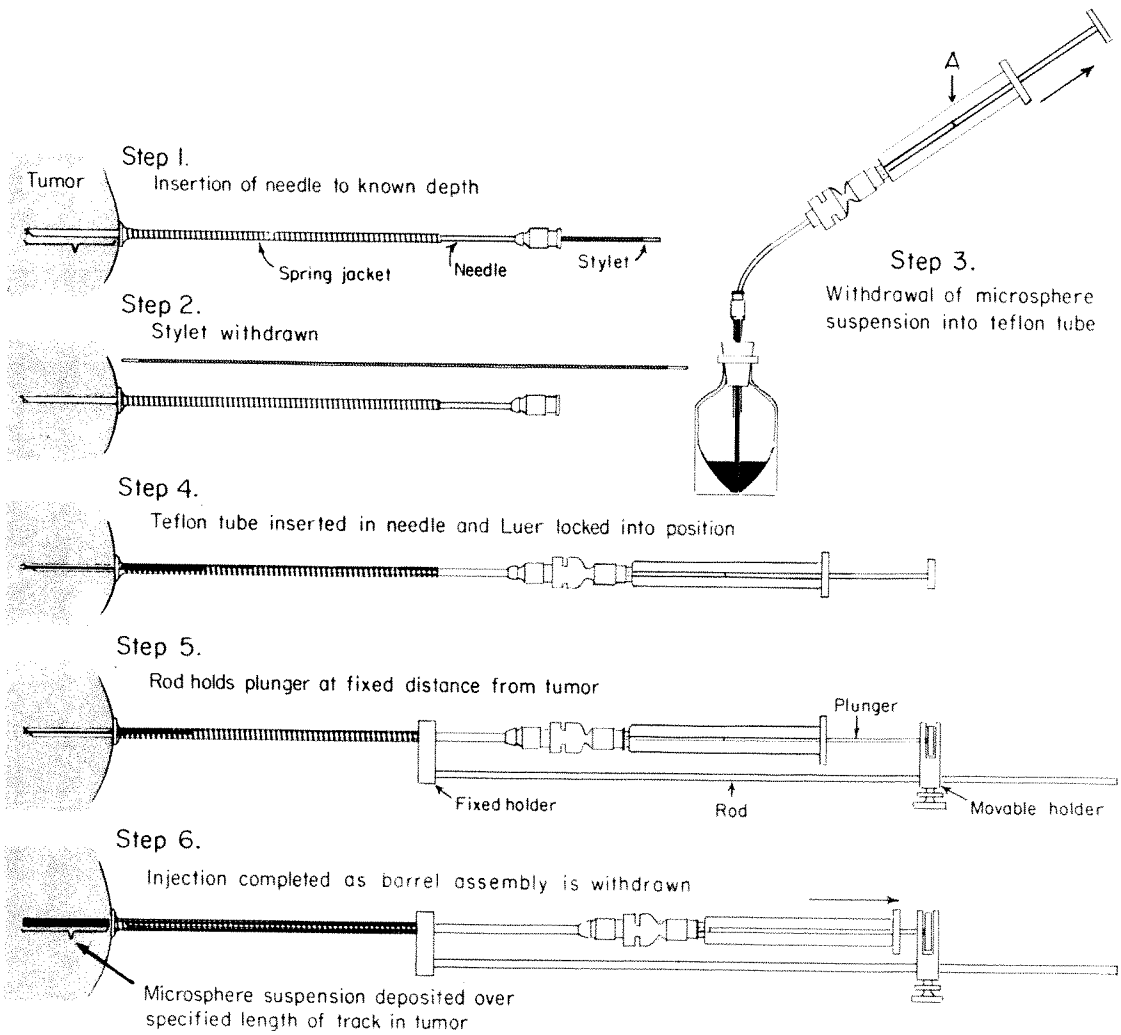

Fig. 4. Steps of implantation (semidiagrammatic).

depth of the needles in tissue at insertion can be determined by simple arithmetic based on the known lengths of the needles and the spring jackets. Anteroposterior and lateral roentgenograms are taken to check the position of needles. The position of the needles is corrected if indicated.

After the procedure has been completed, conventional nuclear medicine diagnostic equipment can be used to produce pictorial displays of the radionuclide distribution (Fig. 5; and 6). They provide rough semiquantitative information regarding anatomic localization of the volume undergoing irradiation.

INITIAL CLINICAL APPLICATIONS

This method, after preliminary testing in laboratory animals, has been employed for the treatment of patients with advanced or recurrent malignant tumors of the tongue, lip, orbit and rectum. Gratifying

Fig. 5. Scintiphotograph of a radioactive microsphere implant—carcinoma of tongue, anteroposterior view.

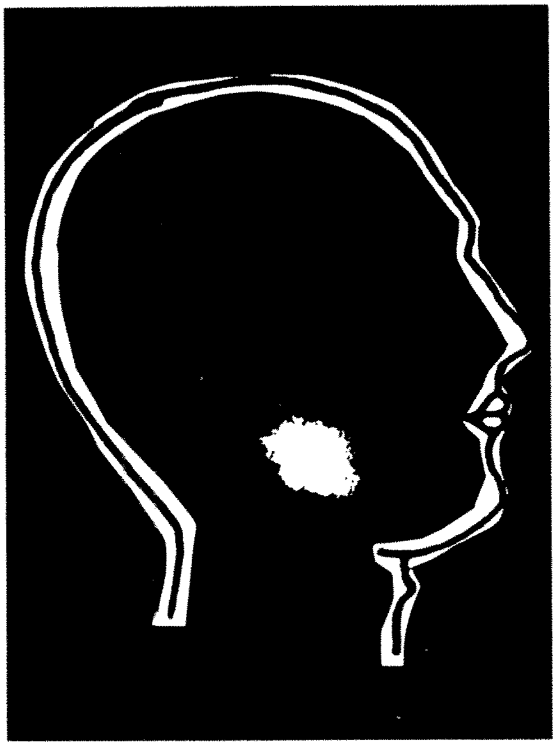

Fig. 6. Scintiphotograph of same patient as in Figure 5, lateral view.

regression of the lesions and relief of pain was obtained in all patients. None could have been managed effectively by any other radiotherapeutic means either because of prior irradiation, limiting anatomic factors, or both. So far, the technique has been used to fill a gap in the radiotherapeutic armamentarium. As experience is accumulated and facility acquired, other indications will be explored.

SUMMARY

There are problems inherent in the currently employed methods of interstitial implantation of radioactive materials for therapeutic purposes. To eliminate some of these difficulties, a new uncomplicated technique has been developed and is here described. Advantages of the method are: (1) the implant is permanent, (2) the radioactive sources are nonmetallic and are not rigid, (3) the procedure can be employed in relatively inaccessible sites, and (4) the dose to the operator and operat-

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This method has been found to be especially valuable in debilitated patients and in those with lesions difficult to treat by conventional means because of anatomic factors, prior radiation therapy, or both.

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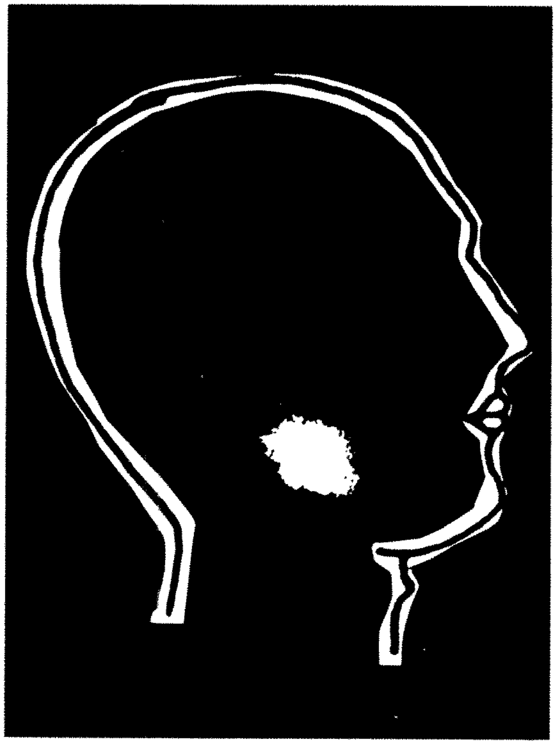

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FIELD SEPARATION IN MULTIPLE PORTAL RADIATION THERAPY*

By DWIGHT W. GLENN, M.S., FRED L. FAW, M.S., A. ROBERT KAGAN, M.D., and RALPH E. JOHNSON, M.D.
BETHESDA, MARYLAND

A SERIES of adjacent treatment portals is commonly employed in external beam radiotherapy, such as in the systematic irradiation of the lymphatic chain for patients with lymphomas or testicular tumors (Fig. 1). Such treatment techniques may involve the junction of fields in several areas with vastly different anatomic considerations regarding the depth of the target (tumor) volumes. In positioning the treatment portals on the skin surface, the adjoining margins may conceivably be overlapped, abutted, or separated depending on various circumstances. (Angled fields[4] are not considered here since this method is impractical with more than 2 fields in sequence.)

It is generally recognized that isodose distributions within an irradiated volume tend to "bulge out" at the margin of the fields as a consequence of beam divergence and side scatter. Although more significant with low energy radiations, this "bulging" is nonetheless appreciable with cobalt 60 and 2 Mv. peak beams as will be discussed. Cognizance of these physical characteristics has led many radiotherapists to adopt a separation of fields. A standard gap of 1 cm. is often employed, regardless of field size or depth of the target volume, and the radiotherapists at some institutions frequently abut the adjoining margins "just to be sure we don't have a cold spot." We have recently completed an extensive review of the radiologic literature which failed to provide specific guidelines or procedures for determining the amount of field separation for various treatment conditions. As will be discussed in this paper, the failure to give precise attention to this matter may either result in complications from undesirable overdosage of normal tissues in the irradiated volume or may produce underdosage in an area potentially involved with tumor. The physical and clinical considerations related to the separation of fields in multiple portal external beam radiotherapy are described in the following sections.

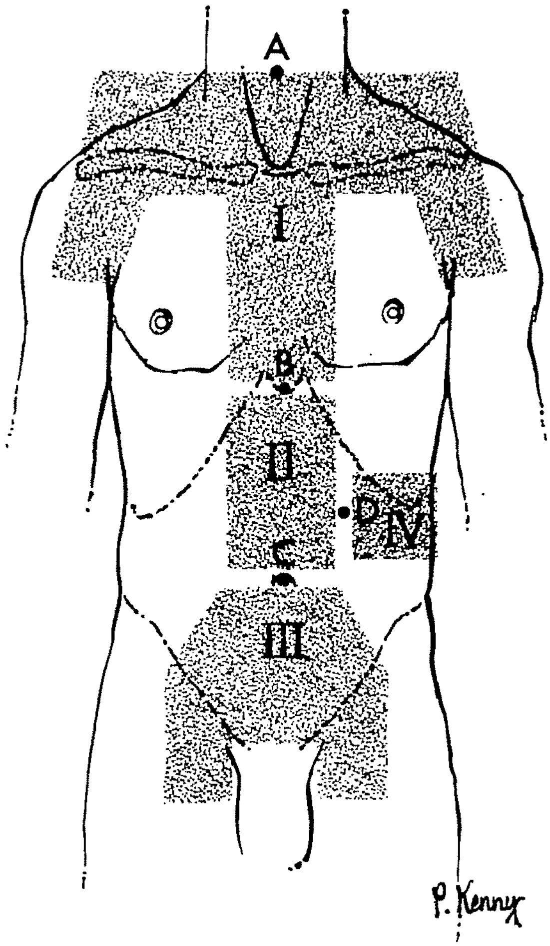

Fig. 1. Multiple anterior fields for lymphomas and Hodgkin's disease.

* From the Radiation Branch, National Cancer Institute, National Institutes of Health, Department of Health, Education and Welfare, Bethesda, Maryland.

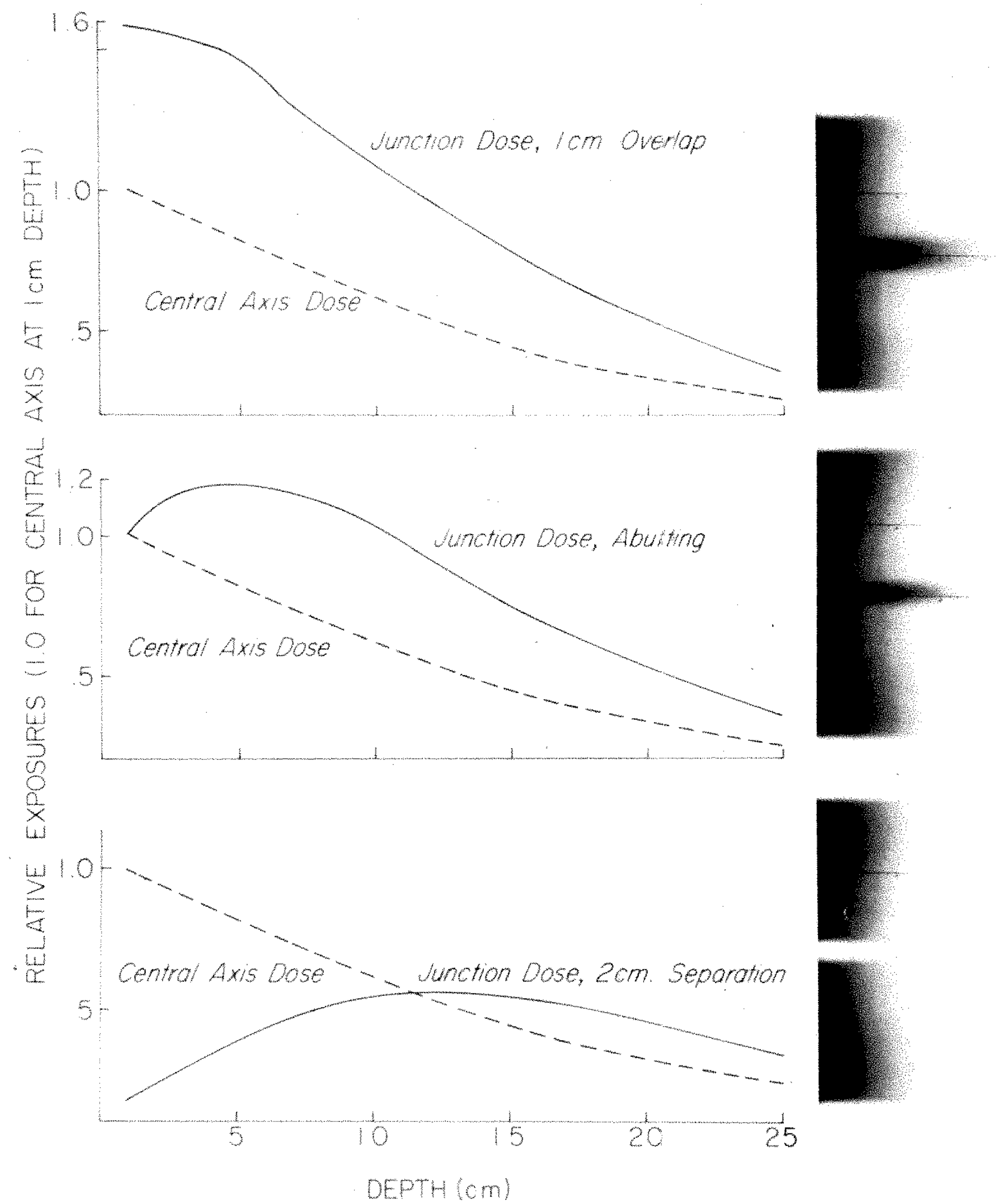

FIG. 2. Comparison of central axis depth dose to junction doses of two cobalt 60 15×15 cm. fields with 1 cm overlap, abutting, and 2 cm. separation of field edges.

MULTIPLE FIELD DOSE DISTRIBUTIONS

Figure 2 compares central axis depth dose with the depth dose at the junction of two cobalt 60 15×15 cm. fields with 1.0 cm. overlap of field edges, abutting field edges and with a 2 cm. separation, using tangentially irradiated Adlux film and lithium fluoride dosimeters. From Figure 2, one sees that overlapping results in high doses at the junction and, moreover, the dose at the desired depth (12 cm. in the illustration) at the junction is approximately 70 per cent more than the dose on the central axis at the same depth. The abutting fields do not drastically alter the "hot spots." It is only when the fields are

separated that hot spots are reduced and doses at the junction are similar to central axis doses for the 12 cm. depth in the example. Note from Figure 2 that the junction dose for separated fields is 50 per cent less at 5 to 6 cm. and does not approach the central axis dose until the desired depth. The hot spots at depth are the result of beam divergence and side scatter causing the isodose distributions to bulge out. The bulging is lengthwise as well as widthwise and the lack of three dimensional dose distributions may explain the readiness to abut or overlap. In using field separations, we are usually considering "lengths" of fields and this is generally the missing dimension of an isodose curve. For example, Field II of Figure 1 may be 10 cm.×15 cm. and the usual isodose curve one consults would be 10×15 cm., but we are interested in the separation at B and C and therefore need the 15×10 cm. isodose curve as well as the curves giving the "lengths" of Fields II and III. For the separation at D of Figure 1, we would need curves giving the "widths" of Fields II and IV.

In this paper we will discuss field "widths," where, in reality, they may be "widths" or "lengths" depending on one's viewpoint. The important thing to realize is which dimension must be considered in determining the field separation.

CALCULATIONS

The calculations to determine field separation are fairly simple if one has isodose curves for the appropriate source-to-skin distance (SSD) and field sizes. Or, in some instances, it may be sufficient to use geometric divergence calculations. In both cases, the purpose is to achieve doses at field junctions that are comparable to the central axis dose at some desired depth. If the total central axis dose at, say 10 cm. depth, is 4,000 rads, then the junction dose at 10 cm. depth should also be 4,000 rads. If the total central axis dose is unequal for the two fields, say 4,000 rads for one and 3,000 rads for the other, then the dose at the junction will be the average, *i.e.*, 3,500 rads.

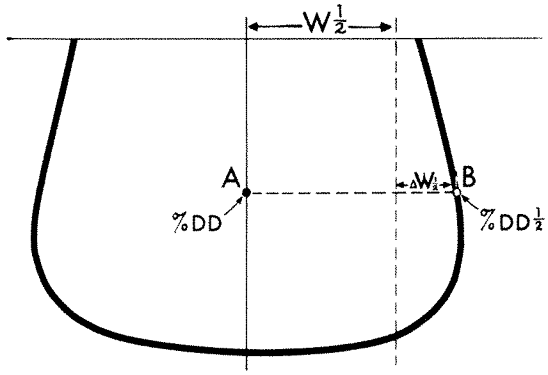

Fig. 3. Arbitrary isodose line depicting "delta half-widths."

In Figure 3 an arbitrary isodose line is depicted. Half of the linear dimension of the geometric field is given as $W\frac{1}{2}$ and the parallel projection with depth is shown as a dotted line. Line AB (perpendicular to the central ray) is the distance from the central ray to where the per cent depth dose at A is halved. The separation contribution from one field is shown as $\Delta w\frac{1}{2}$ (delta half width). Figure 4 depicts two fields so positioned that the dose at B is equal to, or the average of, the dose at A and "a." Here, A, B, and "a" are at the same depth. Lower case letters are used for the right isodose line to indicate that these values may be different than those for the left. The total separation on the surface is the sum of the delta half-widths, *i.e.*, $\Delta W\frac{1}{2}+\Delta w\frac{1}{2}$. This procedure is essentially what we do with isodose transparencies, *i.e.*, shift the transparencies so the doses at A and B are equal, then measure the distance between the central rays or field edges to determine surface separation.

Using the isodose curves of interest, one can measure the delta half-widths from 5 to 15 cm. at 2 cm. increments. By plotting $\Delta w\frac{1}{2}$ *vs.* depth, one should have a family of straight lines for each SSD, allowing interpolation for depth or field size. (These lines are the 50 per cent "decrement lines" as discussed by Orchard[5].) Figure 5 is a plot of $\Delta w\frac{1}{2}$ *versus* depth for various fields for the AECL Theratron 80 unit* at an SSD of 80

* Atomic Energy of Canada Ltd., Ottawa, Ontario.

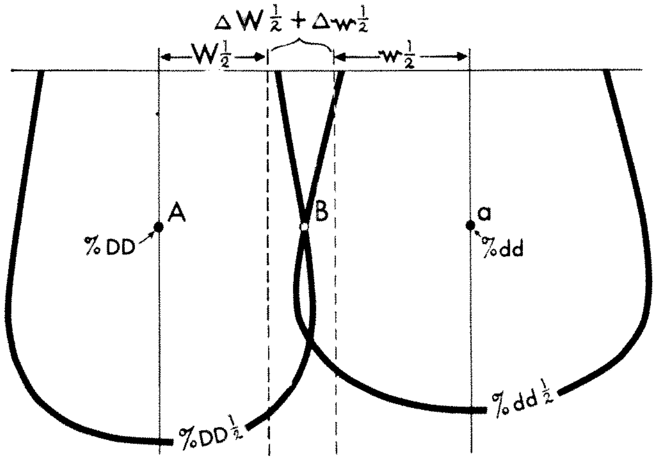

FIG. 4. Adjoining isodose lines showing required separation so doses at points A, B, and "a" are equal or B is the average of A and "a."

cm. Note that only one dimension is given for the fields since it can be shown that the delta half-widths do not change with the other field dimension. To obtain the separation for two fields, one adds the $\Delta w\frac{1}{2}$s of each. For example, two fields 15 cm. and 25 cm. long are used to treat to a depth of 10 cm. From Figure 5, the $\Delta w\frac{1}{2}$ for the 15 cm. field is 1.1 cm. and that of the 25 cm. field 1.7 cm., giving a total separation of 2.8 cm.

As mentioned previously, one could use separations based on the calculated divergence of the geometric field. The error in this method depends on the particular unit since the amount of separation varies with SSD, source size, collimating system, etc. Whether this error is as great as using isodose curves is a moot question, since many isodose curves in use have been calculated or have been measured with relatively large ionization chambers where, in the region of the steep dose gradients under consideration, specific dose levels are difficult to localize. The cobalt 60 isodose curves used herein were measured with a 0.4 cm. diameter ionization chamber. Table 1 indicates the difference in the two methods, *i.e.*, curve measurements or divergence calculations where the equations for $\Delta w\frac{1}{2}$ (as a function of depth D) were calculated by the least-squares method from isodose curve measurements, and $\Delta g\frac{1}{2}$ indicates the separation based on geometric divergence only.

Table 1 indicates that for most applications the differences would be small, the larger differences being for shorter treatment distances and large fields, *e.g.*, a 0.9 cm. difference for a field length of 25 cm. at an SSD of 60 cm. and a depth of 15 cm., but only a 0.2 cm. difference for a field length of 10 cm. at an SSD of 80 cm. and a depth of 10 cm.

EXPERIMENTAL RESULTS

To verify the calculations above, two dosimetric models were utilized. The first

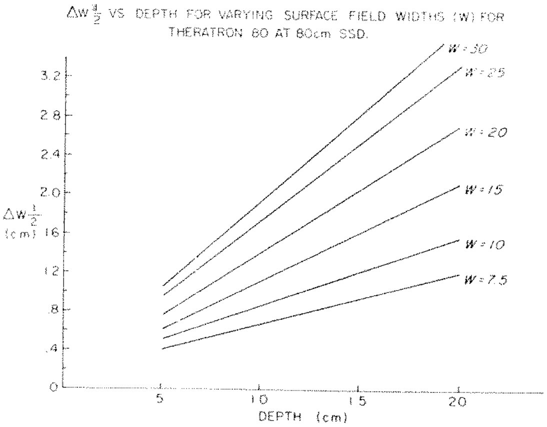

FIG. 5. Delta half-widths *versus* depth for various fields for the AECL Theratron 80 unit, 80 cm. source-to-skin distance.

Table I

COMPARISON OF SEPARATION EQUATIONS AS A FUNCTION OF DEPTH (D) FOR THERATRON 80

SSD \ Field Length	10 cm.	25 cm.
60 cm.	$\Delta w\frac{1}{2}=0.15+0.085D$ $\Delta g\frac{1}{2}=0.083D$	$\Delta w\frac{1}{2}=0.09+0.221D$ $\Delta g\frac{1}{2}=0.208D$
80 cm.	$\Delta w\frac{1}{2}=0.146+0.07D$ $\Delta g\frac{1}{2}=0.0625D$	$\Delta w\frac{1}{2}=0.140+0.158D$ $\Delta g\frac{1}{2}=0.156D$
100 cm.	$\Delta w\frac{1}{2}=0.09+0.067D$ $\Delta g\frac{1}{2}=0.05D$	$\Delta w\frac{1}{2}=0.05+0.139D$ $\Delta g\frac{1}{2}=0.125D$

was done by sandwiching DuPont Adlux film between layers of tempered pressdwood (masonite). The dimensions of the pressdwood phantom were 51 cm.×51 cm.×30 cm. With the beam perpendicular to the film surface, exposures were made with appropriate field separations for the depth of film position.

The second dosimetric model used was lithium fluoride (LiF) powder in No. 5 gelatin capsules placed in appropriate drilled holes in a Machlett-Alderson Rando phantom. The field separations were made over the lower trunk of the phantom where the less dense lung material was absent.

Using the above two models, data were accumulated from various field size combinations at various depths. Both models gave consistent results: hot spots were eliminated but the dose at the "gap" was lower than the central axis dose as shown by the example in Figure 6. Why the experimental results differ from the calculated expectancy is not apparent but the data collected have shown that all calculated separations are approximately 0.5 cm. too great. It is interesting to note that back extrapolation of the lines of Figure 5 do not pass through the origin. However, experimental results would modify these lines so that they would approximately pass through the origin. With this information, all tabulated separations were reduced by 0.5 cm. and dosimetric verification was made again using film and LiF. There was an improvement in the results. The reduction of dose at the gap was eliminated while hot spots were still much lower than on the abutting or overlapping fields. As shown by Figure 7, the dose at each specific

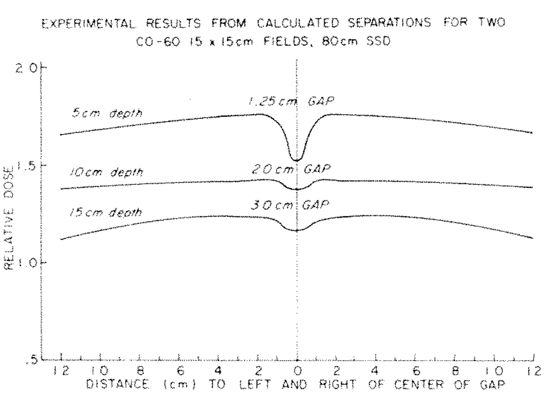

Fig. 6. Experimentally determined dose distributions from calculated data.

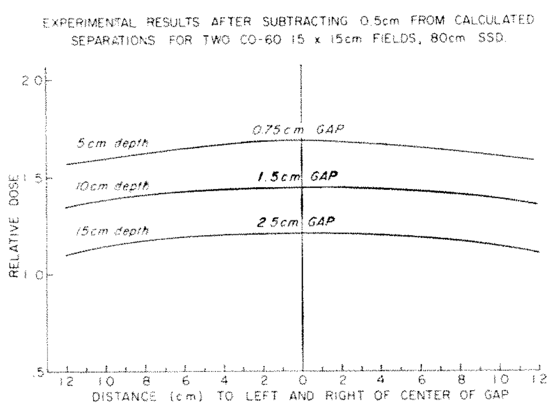

Fig. 7. Experimentally determined dose distributions after subtracting 0.5 cm. from calculated data.

TABLE II

SEPARATION DISTANCE (CM.) BETWEEN FIELDS, THERATRON 80, 80 CM. SSD

Field Lengths (cm.)* \ Depth (cm.)	5	6	7	8	9	10	11	12	13	14	15
10–10	.50	.50	.75	.75	1.00	1.00	1.25	1.25	1.50	1.50	1.75
10–15	.50	.75	1.00	1.00	1.25	1.25	1.50	1.75	1.75	2.00	2.00
10–20	.75	1.00	1.25	1.25	1.50	1.75	2.00	2.00	2.25	2.50	2.75
10–25	1.00	1.00	1.25	1.50	1.75	2.00	2.25	2.50	2.75	3.00	3.00
10–30	1.00	1.25	1.50	1.75	2.00	2.25	2.50	2.75	3.00	3.25	3.50
15–15	.75	.75	1.00	1.25	1.50	1.50	1.75	2.00	2.25	2.50	2.50
15–20	.75	1.00	1.25	1.50	1.75	2.00	2.25	2.50	2.75	3.00	3.00
15–25	1.00	1.25	1.50	1.75	2.00	2.25	2.50	2.75	3.00	3.25	3.50
15–30	1.00	1.25	1.75	2.00	2.25	2.50	2.75	3.00	3.25	3.50	3.75
20–20	1.00	1.25	1.50	1.75	2.00	2.25	2.50	2.75	3.00	3.25	3.50
20–25	1.25	1.50	1.75	2.00	2.25	2.50	2.75	3.25	3.50	3.75	4.00
20–30	1.25	1.50	2.00	2.25	2.50	2.75	3.00	3.50	3.75	4.00	4.25
25–25	1.25	1.50	2.00	2.25	2.50	3.00	3.25	3.50	3.75	4.25	4.50
25–30	1.50	1.75	2.00	2.50	2.75	3.25	3.50	3.75	4.00	4.50	4.75
30–30	1.50	2.00	2.25	2.50	3.00	3.50	3.50	4.00	4.25	4.75	5.00

* Lengths of fields perpendicular to their adjoining edges. A larger listing may be obtained from the senior author.

depth is fairly homogeneous over the entire length of both fields and no apparent gaps are seen.

Table II indicates our field separation values as calculated and modified by experiment. This Table is used only for our Theratron 80 unit at an SSD of 80 cm. This unit has penumbra trimmers adjustable to 45 cm., 55 cm., and 65 cm., but no significant difference was found on field separation values as to trimmer position. Note that only field "lengths" are given, *i.e.*, "lengths" perpendicular to their "adjoining" edges. These "lengths" are usually parallel with the long axis of the body except for the spleen and para-aortic fields.

CLINICAL ASPECTS

The following two cases serve as illustrations of the importance of selecting the proper separation for two adjacent treatment portals.

CASE I. This 58 year old white male with Hodgkin's disease presented with generalized lymphadenopathy above and below the diaphragm, anemia, and a history of significant weight loss. Following completion of radiotherapy to the cervical and mediastinal lymph nodes ([illegible],600 rads in 21 days) through a single anterior field, irradiation of the para-aortic lymph nodes was begun using an anterior field. The upper margin of this latter treatment portal directly abutted the lower margin of the mediastinal field. The para-aortic lymphatic chain received a dose of 3,400 rads delivered in 17 days using the central axis depth dose calculation. Two months after completion of radiotherapy, the patient developed upper gastrointestinal symptoms. Three distinct ulcers were roentgenographically demonstrated in the antrum of the stomach (Fig. 8). Conservative medical management was given, the symptoms subsided, and a subsequent upper gastrointestinal series was reported as showing healing of the ulcer craters. One and one-half years later, the patient experienced painless upper gastrointestinal bleeding requiring several blood transfusions. Rigid medical management was again undertaken and the patient is now asymptomatic nearly 2 years after completion of radiotherapy.

Comment. In review, the junction of the cervicomediastinal and para-aortic fields was seen to overlie the epigastrium with a calculated junction dose of 4,950 rads at the depth of ulceration. As reported by

others,[1–3,6] this dose exceeds that safely tolerated by the gastric mucosa. Such radiation ulcers are usually refractory to medical care and require surgical resection.

Case II. This 36 year old white female with Hodgkin's disease presented with cervical and mediastinal lymphadenopathy and a history of fever, night sweats, and generalized pruritus. Evaluation of the infradiaphragmatic lymphatic chain was incomplete in that a lower extremity lymphangiogram could not be performed because of a possible hypersensitivity to iodine. Irradiation was carried out to the cervical, axillary, mediastinal, and para-aortic lymph nodes. The cervicomediastinal field encompassed a large tissue volume, necessitated by the marked upper mediastinal lymph node involvement. The lower margin of the mediastinal field was at the lower limit of the roentgenographically involved mediastinal lymph nodes. There was a 2.5 cm. skin separation between the mediastinal and para-aortic portals. This varied from our standard procedure of including all mediastinal and hilar lymph nodes in a single treatment field. The patient remained clinically free of disease for slightly over 1 year when a lateral roentgenogram of the chest demonstrated a rounded substernal mass.

Fig. 8. Case I. Upper gastrointestinal series demonstrating multiple gastric ulcers (arrows).

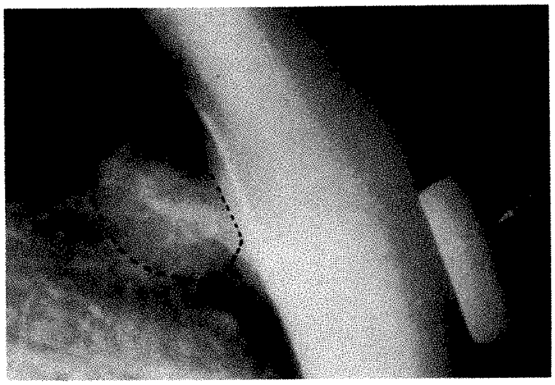

Fig. 9. Case II. Lateral chest roentgenogram showing recurrent disease beneath the gap.

Comment. As shown in Figure 9, where the lead block indicates the position of the gap between fields, the recurrence is located at the margin of the field separation. For this reason, we consider separation of treatment portals contraindicated with supervoltage when potentially involved tumor volumes are present at a depth of 5 cm. or less below the skin surface.

DISCUSSION

Prior to the advent of supervoltage radiotherapy, the intolerance of the skin to intensive daily or total radiation doses limited to some extent the problem of damage to internal organ systems. The "skinsparing effect" of modern equipment has focused attention on the deep-seated normal tissues and the literature is replete with accounts of such radiation complications. With cobalt 60 teletherapy or 2 Mv. peak roentgen therapy, the dose between fields in depth may be up to 70 per cent higher than the central axis dose for abutting external treatment portals.

As illustrated, it is preferable to avoid field junctions directly over regions of known or potential tumor involvement unless the depth of the target volume is greater than 5 cm. In the latter instance, it is possible to select proper field separations to obtain a homogeneous tumor dose at depth without concomitant overdosage of the overlying normal tissues. The routine use of field separations as described has re-

sulted in a 75 per cent reduction in the incidence of serious gastric complications in our experience.

SUMMARY

A series of contiguous treatment fields is frequently used in radiotherapy, as with irradiation of the lymphatic chain for testicular tumors and lymphomas. With the desire to deliver a homogeneous dose to target volumes in depth, it is necessary to place adjacent treatment portals on the skin surface in such a manner that "hot" spots in normal tissue areas and "cold" spots in tumor volumes are avoided.

A method of separating fields is presented where isodose curve measurements or geometric calculations are modified by experiment, using lithium fluoride and Adlux film in phantoms. It is shown that these separated fields, while giving homogeneous doses in depth, avoid high doses to overlying regions. Examples are described to illustrate the clinical importance of these considerations.

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PHOTOGRAPHIC TECHNIQUE FOR LEAK TESTING RADIUM SOURCES*

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TO USERS of sealed radium 226 sources and to personnel of radiation control agencies, who are responsible for public health, a quick, reliable method for determining if sources are leaking is extremely important. As the frequency of testing the sources (Fig. 1) for leakage is increased, the probability of discovering faulty ones and being able to take proper action before radioactive contamination or health hazards occur is also increased. Unfortunately, no rapid, dependable method exists for leak testing radium 226 sources. Many of the current techniques generally require that the source be placed in a leak tight chamber for periods up to 24 hours, after which time the chamber is examined for radium and daughter products resulting from the leak. Examples of such tests include the Hale[3] method in which the leaking source is placed in a stoppered test tube containing 5 ml. of tap water with 0.37 gm. of activated charcoal. After 24 hours, the source is removed and 24 hours later the stoppered test tube is placed in a well scintillation counter.

Other techniques which offer variations of the Hale method include the cotton plug and jar test systems.[1,4] In the first of these 2 procedures, the leaking source is placed in a sealed test tube or bottle for 24 hours with a wad of cotton. After this period, the cotton is removed and measured for radioactivity by a G-M survey meter. In the jar test, the inside surface of the screw-top lid is examined with an alpha survey meter after the source has been sealed in the jar for 24 hours.

Gallaghar and others perfected an electrostatic technique.[2] In this method the radium source is placed in a sealed cylindrical chamber having electrodes at either end across which a 300 volt DC potential is applied. Because radioactive decay of radium tends to create positively charged daughter products, most of these products are deposited on the cathode where they can be measured by a G-M counter. The period of collection ranges from a few minutes to several hours.

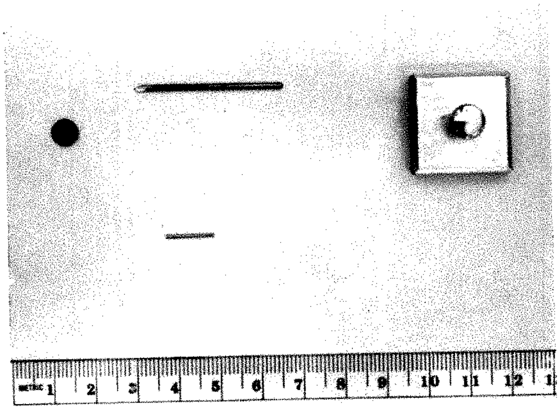

Fig. 1. Examples of sealed sources of radium 226 as shown from left to right include: 2.5 mg. plaque; 15 mg. needle; 5 mg. cell below; and 10 mg. plaque.

These techniques are hindered not only by the long period required for sample collection, but also by the need for either radiation survey meters or laboratory detection instruments to determine the presence of radioactive leakage. In addition, results from many of these tests are frequently unreliable and may be misleading.

Because of the disadvantages in current leak testing methods, the Radium Technology Unit at the Southeastern Radiological Health Laboratory has conducted preliminary investigations of a photographic method. The essence of this new procedure is the ability of alpha particles to interact with a zinc sulfide (ZnS) scintil-

* From the U. S. Department of Health, Education and Welfare, Public Health Service, Southeastern Radiological Health Laboratory, Montgomery, Alabama.

lator, thereby producing light which can be recorded by high speed photographic film.*

In the decay chain of radium several alpha, beta and gamma emitters are produced. Since alpha particles cannot penetrate the walls of a sealed source, it is obvious that their detection external to the source is evidence of a leaking or contaminated source. One way, therefore, of determining if a leak or contamination exists, is to look for alpha emitters outside of the source. This can be done almost instantly with the photographic technique.

EXPERIMENTAL

As the major objective of the photographic technique is to detect light produced only by the alpha-ZnS interaction in a mixed radiation field, it was necessary to evaluate the extent to which beta and gamma radiation might also produce light. For this purpose, experiments were conducted using 2 leaking Ra^{226} plaques, 2.5 mg. and 5.0 mg., and a 3 mc Co^{60} source. Each source was tested separately by placing the source in a 2 inch glass Petri dish, which is opaque to alpha particles, and placing the dish on a piece of ZnS coated plastic screen with the ZnS facing the source. The source, dish, and ZnS were arranged with a simple lens and a Polaroid 4×5 Land film holder assembly so that the image formed on the ZnS sheet by the radiations from the source could be photographed. The experiments were repeated with the sources placed directly on the ZnS without the Petri dish. Comparison of the images showed conclusively that the ZnS emitted light not only when it was exposed to alpha particles but also to beta-gamma radiations and particularly to beta. The comparison, however, also indicated that the alpha contribution in an alpha-beta gamma field could be easily discriminated by a shielding material. In addition, experiments were conducted to improve the scintillator's response to alpha particles in the presence of beta radiation. The ZnS screen, which was obtained commercially and which contained about 10 mg. ZnS salt mixture/cm.², was treated with 12*N* HCl for 30 minutes or until the salt concentration on the screen reached 5 mg./cm.² This modification of the scintillator reduced the beta effect on the ZnS, thereby highlighting the alpha contribution.

* For the experimental studies in this investigation, Polaroid Land film ASA 3,000 type 57 in the Polaroid 4×5 Land film packet system was selected. The film holder in this system is lightweight and its cost is under 50 dollars. Use of this equipment does not constitute an endorsement by the Public Health Service.

Based on these preliminary findings, a more efficient photographic system was devised which included a device to properly orient the source to the ZnS and film. A schematic diagram of this system (Fig. 2) is shown together with explanatory terms.

In operation, two foot tongs are used to place the source in the 20 pound lead sample chamber. The source is laid on the alpha absorber (plastic-8 mg./cm.²) overlying a ZnS screen which rests on a thick piece of plexiglass (1.6 gm./cm.²). This

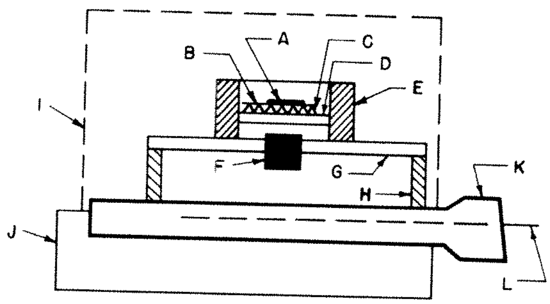

Fig. 2. Schematic diagram of the photographic lens system showing the lead sample chamber in relation to the lens and the film holder.

The various components of the system are as follows:

A. Source
B. Movable alpha absorber (plastic—8 mg./cm.²)
C. Movable ZnS screen
D. Plexiglass sample support (1.6 gm./cm.²)
E. 20 pound lead shield sample chamber assembly
F. 10× ocular lens
G. Sliding wooden platform
H. Supporting tracks for platform and chamber
I. Light-tight lid
J. Wooden base
K. Film holder
L. Film—4×5 packet

chamber assembly is supported by a sliding platform and rests directly over a 10× microscope ocular lens. The chamber, platform and lens are fixed together and may be moved from side to side as a single unit over the film holder. When the source is in place, the light-tight lid is closed and a 4×5 film packet is slipped into the film holder. In making the exposure, the protective envelope of the film is pulled outward from the holder but not removed completely from it. The plastic shield over the ZnS prevents the alpha particles from interacting with the ZnS and the film records light produced only by the interaction of beta and gamma radiations with the scintillator. The light is focused through the lens and a well defined image is formed on the film. The protective envelope is replaced, the light-tight lid opened and the sample platform moved over to the next exposure position. In this new position, the plastic shield is removed and the source is placed in direct contact with the ZnS surface. The exposure procedure is repeated for the second picture. In this manner, 2 different exposures are made on the same film. (By slight alterations in the design of the sample platform, many more exposures can be made on a single film.) For the shielded situation, only the beta-gamma interactions on ZnS are produced. In the unshielded case, the alpha and beta-gamma effects are photographed. By comparing the 2 images, the alpha contribution can be seen. This technique, which requires about 3 minutes for each exposure and 10 seconds for development of the print, can detect point sources of radium contamination or leaking radium or exposed radium as low as 500 picocuries in medical sources ranging up to 50 mg. of radium. The limit of detectability was evaluated experimentally by photographing various levels of unsealed radium in conjunction with different sources. In addition, dosimetric measurements indicated that a person using the photographic technique in testing ten 10 mg. needles during a period of 1 hour would receive about 2 mr whole body exposure and about 15 mr to his hands.

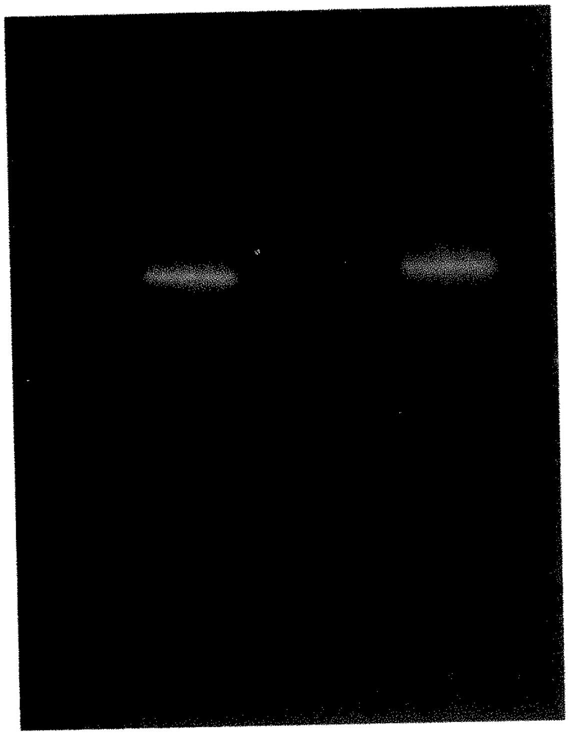

Fig. 3. A dual exposure of a 5 mg. cell which registered essentially no alpha activity in the jar test determination. The exposure time was approximately 3 minutes for each picture. For image on left, the cell was unshielded. For image on right, the cell was shielded from the ZnS by an alpha absorber (plastic—8 mg./cm.^{2}). The images are practically alike and, therefore, indicate no radium leakage or contamination above 500 picocuries, the detectable limit of the photographic method.

Interferences in the photographic method were found to be minor. No significant amount of direct film exposure resulted from the gamma rays associated with the leakage material or the source itself. This was probably due largely to the position of the source during an exposure (about 11 cm. above the film) and of the film's relative insensitivity to gamma radiation as corroborated by Co^{60} irradiation experiments. Beta radiation from the source, however, did cause general fogging of the film. This effect was eliminated by using a thick piece of plexiglass (1.6 gm./cm.^{2}) as the sample support.

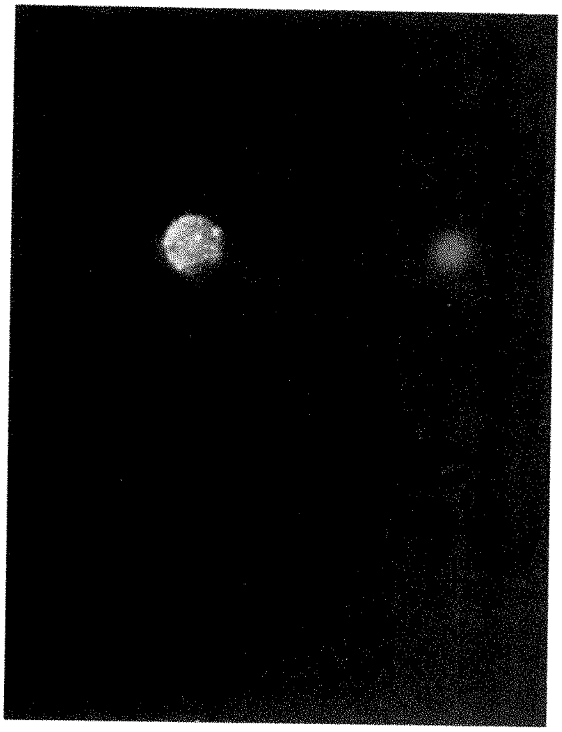

Fig. 4. Exposures of an unshielded and shielded leaking 2.5 mg. radium 226 plaque which showed an alpha activity of 500,000 cpm by the jar test. The 3 minute exposures show a marked difference in the images as well as the location of point sources of exposed radium and daughter products on the plaque.

RESULTS AND CONCLUSIONS

Qualitative experimental results can be readily seen in pictures beginning with Figure 3. The image on the left in all the leak-test photographs represents the effects of all external radiation produced by the source and the right hand image is formed by all external radiation except alpha. The significant difference between the 2 images, which are magnified approximately 1 1/2 times, is due, therefore, to the alpha radiation as produced by a leaking or contaminated source. As it applies to the photographic method, a leaking source is one which is releasing or exposing radium 226.

As an example of what a nonleaking radium source (Fig. 3) would look like, a 5 mg. cell was used in the unshielded and shielded positions. It is evident in comparing these pictures, that there is little or no difference between the images. From this observation, it is possible to conclude that the source is not contaminated or leaking radium, at least above the 500 picocurie limit as established for the photographic method. In contrast to this, a 3 minute exposure (Fig. 4) of a 2.5 mg. radium plaque, which registered over 500,000 cpm by the jar test, depicts the leaking and contaminated nature of the source quite well. The reverse side of the 2.5 mg. plaque (Fig. 5) which was purposely contaminated shows the distribution of contaminants despite the strong beta-gamma background.

A badly leaking 5 mg. plaque was also tested (Fig. 6) and the results are quite conclusive. This particular source was an obvious leaker because it was noticeably damaged. There are, however, many sources which look good and structurally sound, but leak just as badly as visibly

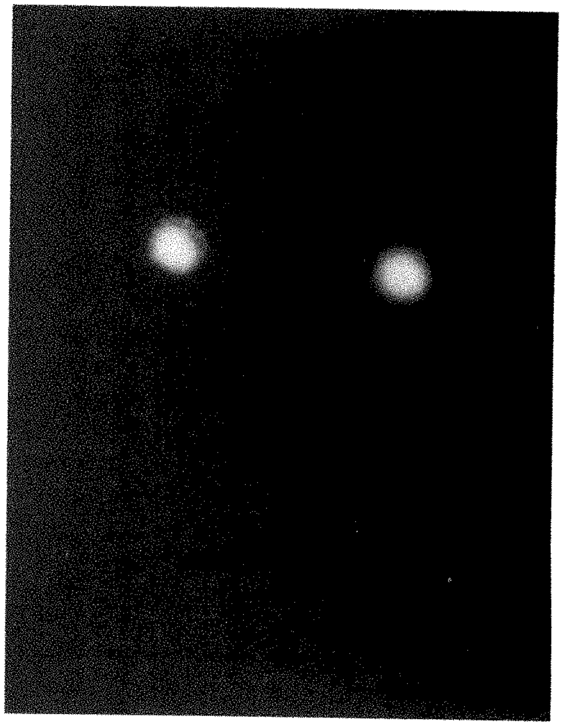

Fig. 5. The contaminated reverse side of the plaque shown in Figure 4. The points of contamination are easily seen in comparing the 3 minute exposures.

broken ones. Two such apparently good cells were examined (Fig. 7 and 8) and found to be leaking or contaminated at various positions along their lengths. Both cells contained about 3 mg. of radium and one which appears badly damaged (Fig. 7) showed about 4,000 cpm in the 24 hour jar test, whereas the other indicated only 300 cpm by the same test.

Studies are continuing at the Southeastern Radiological Health Laboratory to improve the picture quality of the photographic technique, to improve its sensitivity, and to automate the device so that it may be operated with less handling. Additional experiments are in progress in the development of a system which can more easily distinguish leaking sources from those that are only contaminated. The photographic method in its present state represents a qualitative leak testing means which can be applied to several facets of radium usage. It has been used to distinguish sources having various amounts

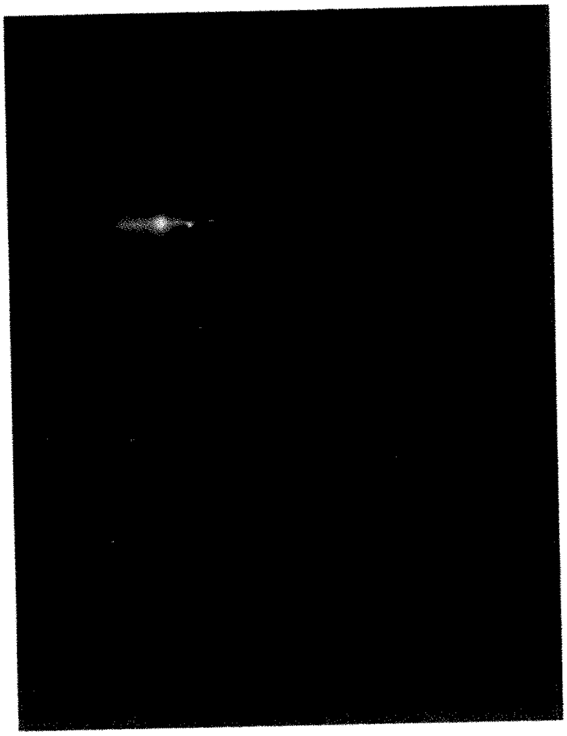

Fig. 7. These 3 minute exposures were made of a 3 mg. cell which appeared to be in perfect condition. The significant difference in the images clearly indicates the leaking or contaminated nature of the source and the area of damage. When measured by the jar test, this source produced 4,000 cpm of alpha activity.

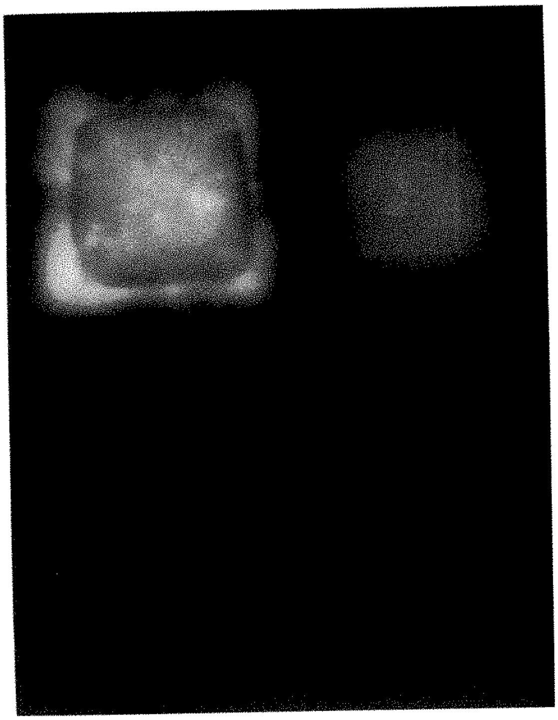

Fig. 6. An extreme difference between the two images is apparent in these 3 minute exposures of a badly damaged and leaking 5 mg. plaque.

of radium from each other and also for detecting radioactive contamination picked up in wipe tests. With proper backlighting (Fig. 9) the photographic system can be easily adapted to assess the distribution of radium within a source. Physicians, radiological health personnel and others will be able to check the integrity of radium sources more frequently and rapidly than is currently possible. Physicians, for example, can quickly examine their sources before and after use in patients and determine at least if they have dangerously leaking or ruptured sources. Since no special instruments are needed to make leak tests by this method, sources can be examined at little cost and readily evaluated at the hospital or in the physician's office. It is also possible to test several sources or make several exposures on a

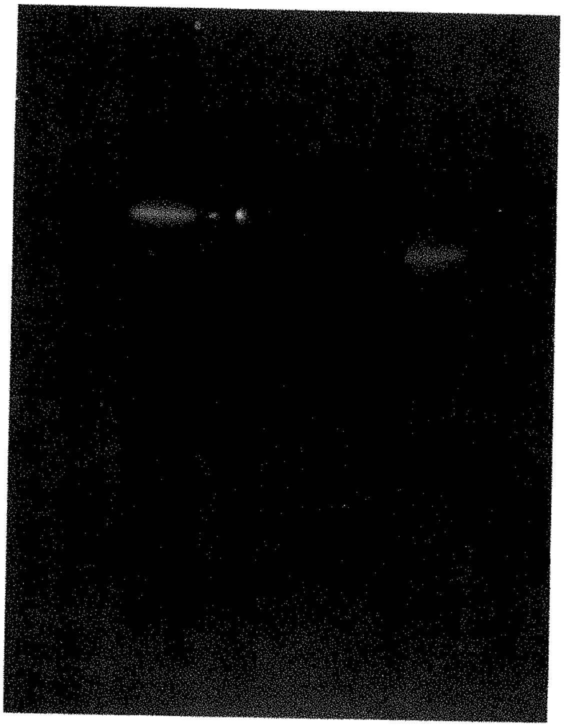

Fig. 8. This 3 mg. cell is similar to the one used in Figure 7 but, as these exposures indicate, the leak is different and is confined primarily at one end. This source produced only 300 cpm of alpha activity when examined by the jar test.

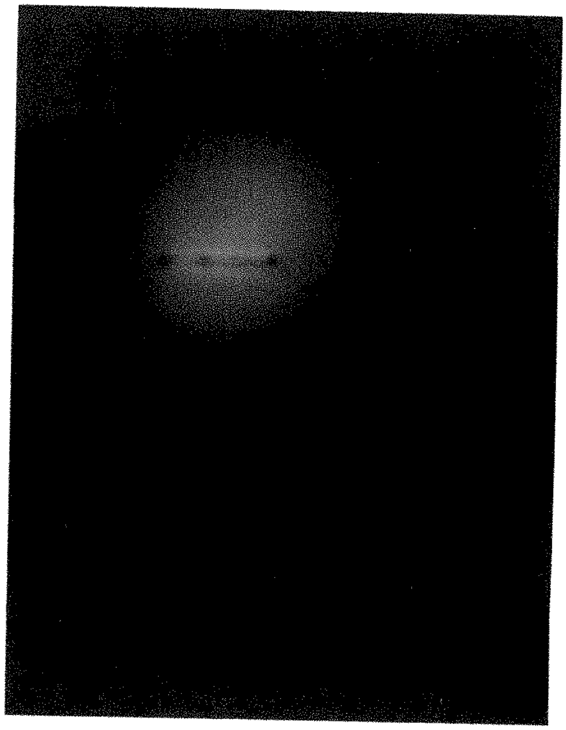

Fig. 9. With proper backlighting, the photographic technique can be easily adapted for use in locating radium 226 within a source. The above picture shows the distribution of radium within a 5 mg. cell.

single film. Contamination of the photographic components or of the sample chamber by leaking sources can be avoided by enclosing the film holder in a disposable plastic bag and by lining the chamber with disposable plastic sheets.

SUMMARY

The photographic method provides a simple, positive and economical means by which radium sources may be regularly and frequently tested for radium leakage and contamination by the user. In this manner, badly leaking sources may be discovered before they cause widespread contamination of buildings, storage facilities or other areas where radium 226 is stored or used. Because of its versatility, its rapid operation and ease of use, the photographic technique represents a safe, effective system which can be used by medical and radiation control personnel for protecting physicians, patients and others against unnecessary radiation exposure.

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"FRACTIONAL LIFE EXPECTANCY" AS A NEW INDEX FOR ANALYZING THE RESULTS OF RADIOTHERAPY*

By K. C. TSIEN
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THE "survival rate" which is at present generally used for expressing the end results of radiotherapy, when properly calculated, is considered to be the best single statistical index available for measuring the efficacy of cancer therapy.[1] While it is true that the duration of survival should be the most telling measurement of response to treatment, in certain areas of cancer therapy, however, it has been of limited use: in breast cancer cases, for instance, the use of survival rates has so far failed to show any significant differences in comparing one form of treatment for breast cancer with another.[2,3,8] This is because the survival rate, which is a percentage measure of a group's characteristics of multiple complexities, is affected by many, many factors, and it is therefore an insensitive index for analyzing any individual factors which may affect the number of survivals for a particular duration.[4] There are further difficulties in studies involving treatment of cancers which are not uniformly in themselves fatal, since in such cases the use of the survival rate for evaluating treatment methods is even conceptually rather unsatisfactory.

In our work at the Temple University Hospital, the survival rates for different types of cancer treated by radiotherapy are routinely calculated by using the life-table method. In Table I a sample of calculation is given for patients with T_1 vocal cord cancer treated by radiation from 1950 to 1964. From this table we obtain the survival rates of this group of patients in terms of the number of years of survival after treatment, but the survival rates do not give us an adequate basis from which to obtain an understanding of the prognosis of the disease. Moreover, these rates are not really representative since the group of patients considered is not statistically a random sample because it consists only of persons who came to or were referred to our hospital.

THE "FRACTIONAL LIFE EXPECTANCY" INDEX

The new index proposed is the ratio of the survival period of each individual patient after treatment to his normal life expectancy according to his population group. Since the normal life expectancy is generally given for different ages of males and females, and also by race in the national vital statistics, it is therefore a fractional life expectancy index (FLE) which automatically takes into account individual variations of age, sex, and race.

Before illustrating the characteristics of this index it must be noted that the concept of comparing the survival experience of cancer patients with that of the general population is not new. As early as 1926 in discussing an objective definition of the success in the treatment of cancer, Greenwood[7] stated: "If an examination of the after histories of such patients showed that on the average they lived as long as a random sample of persons of the same age, sex, occupation, etc., nobody could object to the use of the word cure." In 1936, Nathanson and Welch[9] compared the survival curve for the patients with malignant disease with a "normal" survival curve of the general population. More recently, in 1966, Hayward[8] has used the life table technique to compare the life expectancy of two series of breast cancer patients after adrenalectomy and hypophysectomy. Ederer *et al.*[6] on the other hand, in 1961, derived the relative survival

* Presented at the Forty-ninth Annual Meeting of the American Radium Society, Toronto, Ontario, Canada, May 29–31, 1967.
From Temple University School of Medicine and Hospital, Philadelphia, Pennsylvania.

TABLE I

SURVIVAL RATES OF PATIENTS WITH T_1 VOCAL CORD CANCER TREATED BY RADIOTHERAPY*
(1950–1964)

Interval	Total Alive	Died in Interval	Lost to Follow-up	Withdrawn Alive	Risk of Dying	Proportion Dying	Proportion Surviving	Cumulative Proportion	Standard Error
1	2	3	4	5	6	7	8	9	10
0– 1	131	5	0	0	131.0	.038	.961	96.18	1.67
1– 2	126	0	0	5	123.5	0.000	1.000	96.18	1.67
2– 3	121	4	0	21	110.5	.036	.963	92.70	2.35
3– 4	96	4	0	15	88.5	.045	.954	88.51	3.03
4– 5	77	2	0	16	69.0	.028	.971	85.94	3.44
5– 6	59	1	1	12	52.5	.019	.980	84.30	3.75
6– 7	45	2	0	12	39.0	.051	.948	79.98	4.64
7– 8	31	1	0	2	30.0	.033	.966	77.31	5.19
8– 9	28	2	0	4	26.0	.076	.923	71.37	6.27
9–10	22	1	0	11	16.5	.060	.939	67.04	7.23

* Calculated as of the end of 1966.

rate from the ratio of the survival rate in a group of patients during a specific interval to the expected survival rate. For this purpose they compared the survival rate of the patients with a group similar to the patient group in such characteristics as age, sex, and race, but free of the specific disease under study.

In all the foregoing cases a single index is obtained for a whole group of patients under study, similar to the commonly used survival rate, and before making any calculation the composition of the group of patients has to be determined. The new index which differs from those others in approach is that it is calculated for individual patients instead of for a group. It is also possible to calculate the FLE index at any interval after treatment which is considered clinically important, as for instance at the time of recurrence of the disease originally treated. The study of the radiotherapy results of T_1 vocal cord cancer patients presented below shows how this index can be used.

A STUDY OF THE RADIOTHERAPY RESULTS OF PATIENTS WITH T_1 VOCAL CORD CANCER

T_1 vocal cord cancer is rarely the direct cause of death, although the patient may die from metastasis to other parts of the body or due to other types of cancer subsequently developed. The relatively long period of survival after treatment enables us to illustrate the different indications that can be obtained from a fractional life expectancy study.

This study relates to 131 cases of T_1 vocal cord cancer patients treated by irradiation from 1950 to 1964 at Temple University Hospital and for which, except in 1 case, follow-up data were kept up to the end of 1966. To take into account the status of the patients as at the end of 1966, they have been classified into 4 groups as follows:

1. Patients alive and free of evidence of disease
2. Patients alive but not free from the disease treated or other types of cancer
3. Patients who died from the disease treated, or due to metastasis, or due to other types of cancer
4. Patients who died from other causes and evidence exists that they were free of any type of cancer

It is fully realized that this classification is open to criticism since as several investigators have noted it is frequently

not possible to determine "unequivocally" whether death is entirely due to cancer. Nevertheless, while the above classification may need further consideration, it is evident that if we are to be able to evaluate treatment results, whether or not a patient is free of evidence of the disease treated and of other types of cancer is a yardstick of judgement,[4] and some classification such as that listed above is required.

For the present study we were able to make the above classification on the basis of the follow-up information obtained; this is shown in Table II. Table III shows the number of deaths among these cases due to cancer or due to other causes. Table IV gives the number of patients in these two groups classified according to the range of fractional life expectancy from the time of treatment to the date of death, and this table also gives the number of patients alive with recurrence of disease classified according to the range of fractional life expectancy from the time of treatment to the time of recurrence observed. The normal life expectancy data used are those for the general population in the United States, 1963.[10*]

It is seen from Table IV that irrespective of the cause of death the average FLE indexed for the two groups (died due to cancer and died due to other causes) are not too different: for one it is 0.31 and for the other, 0.35. In addition, for both groups, about 60–70 per cent of the deaths occurred within a period of 0.30 of their respective life expectancy.

* It may be noted here that for greater accuracy the life expectancy data used in each case should be those for the year the patient was treated. Due to the changes of mortality rates in the general population in different years, the life expectancy data are also somewhat different. However, for the purpose of illustrating the use of this index, the variations in this factor are neglected.

TABLE II

PATIENTS WITH T_1 VOCAL CORD CANCER TREATED BY RADIOTHERAPY (1950–1964)

Status December 31, 1966

			Total
Alive	No disease 99	With recurrence 9	108
Dead	Not due to cancer 15	Due to cancer 7	22
			130*

* Excluding 1 case lost to follow-up.

TABLE III

PATIENTS WITH T_1 VOCAL CORD CANCER TREATED BY RADIOTHERAPY (1950–1964)

Died before December 31, 1966

Cause of Death	No. of Patients
Due to cancer	*7*
Metastasis to lung	2
Metastasis to liver	1
Lung cancer	2
Hodgkin's disease	1
Type unknown	1
Due to other causes	*15*
Heart failure and coronary occlusion	5
Cerebral vascular accident	4
Hepatic failure	1
Parkinson's disease	1
CO poison	1
Others	3

TABLE IV

PATIENTS WITH T_1 VOCAL CORD CANCER TREATED BY RADIOTHERAPY (1950–1964)

Status December 31, 1966

Range of FLE	Alive with recurrence*	No. of Patients: Died due to cancer	No. of Patients: Died due to other causes
–.10	8 (89%)	0	4 } (60%)
.11–.30	1	5 (71%)	5 }
.31–	0	2	6
Total number	9	7	15
Average FLE	0.075	0.31	0.35

* FLE (fractional life expectancy) calculated at the time of recurrence observed.

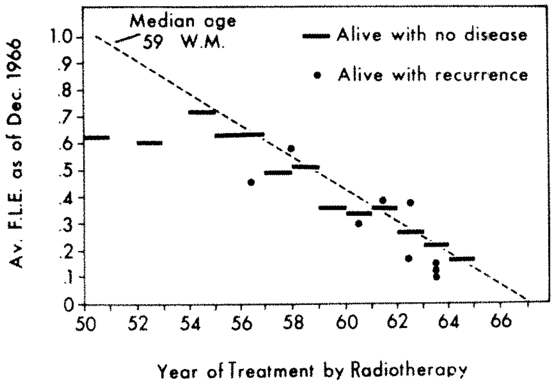

Fig. 1. Graph plotting the average fractional life expectancy (FLE) of the living patients treated each year against the year of treatment.

In the case of patients who had recurrences, as seen in Table iv, nearly 90 per cent of the recurrences took place within a period of 0.10 or less of the normal life expectancy, and the average FLE is 0.075.

The use of this index also opens up new possibilities for analyzing the results of treatment. For instance, if we plot the average FLE of the living patients (calculated up to the end of 1966) treated each year against the year of treatment, we have a graph as shown in Figure 1. This graph comprises two distinct portions: a horizontal portion which lies between years 1950 and 1956, and a regularly descending portion after 1956. The horizontal portion shows that the average FLE for the patients treated from 1950 to 1956 is nearly constant between 0.6 and 0.7. The second portion shows that after 1956 the average FLE decreases nearly linearly, as might be expected, since the FLE is greater for patients treated earlier than those of the same age treated more recently. The FLE of living patients will of course increase as the time goes on until they die. In fact the average FLE indices after 1956 nearly lie on the straight line representing the FLE of a white male of 59 years of age (normal life expectancy 16.5 years) for whatever the year of treatment. The actual median age of the whole series of patients in this study was in fact 59.

In Figure 1, the individual FLE of the patients alive with recurrence of disease were also plotted as of the end of 1966. So far the highest FLE of the patient still alive with recurrence is 0.59, and 5 out of 9 cases now already have a FLE greater than, or equal to, 0.30. This would seem to indicate that the recurrence of vocal cord cancer does not necessarily have any significant effect on the patient's life-span.

Summarizing the above analysis derived from the use of the fractional life expectancy, the life-span of the patients with T_1 vocal cord cancer after radiotherapy may be considered in several different stages, as shown in Figure 2.

(1) Ninety per cent of recurrences took place within 0.10 of the patient's life expectancy at the age when treated.
(2) Sixty to seventy per cent of deaths due to cancer or due to other causes occur within 0.30 of the patient's life expectancy. The high percentage of deaths due to other causes within 0.30 of the normal life expectancy in our group may indicate that these patients admitted for radiotherapy were originally not in good health.
(3) There is an indication that due to the deterioration of general health affected by the disease, the patient's life expectancy may be reduced to 0.6 to 0.7 of the normal life expec-

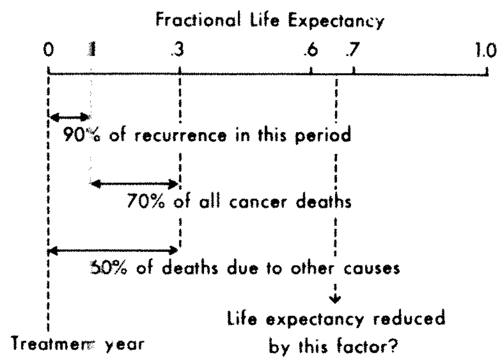

Fig. 2. Barriers in the life-span of T_1 vocal cord patients.

tancy (see the horizontal portion of the graph in Figure 1).

As already shown above, of the cases treated for T_1 vocal cord cancer, 60–70 per cent of the deaths, whether due to cancer or due to other causes, generally occurred at the fractional life expectancy of 0.30 or less. If we take this as a dividing point, the whole group of patients as of the end of 1966 can be further divided into those with a FLE greater than 0.30 and with a FLE equal to 0.30 or less, as shown in Table v. Patients alive or dead, and free of evidence of the original disease treated, each of whose FLE is greater than 0.30, may be tentatively considered as the successful group. Patients alive with recurrence or with other types of cancer, or who have died from cancer may be considered as ineffective control of the disease. Patients for whom the treatment can only be considered as inconclusive are those, alive or dead, whose FLE was 0.30 or less and who were free of evidence of disease and any other types of cancer. It may be reasonably hoped that once a patient lives beyond this period, namely, when his FLE exceeds 0.30, he will have a greater opportunity to live up to 0.6 to 0.7 of his normal life expectancy. Of course, additional data and new studies may either support or disprove this expectation.

Table V

PATIENTS WITH T_1 VOCAL CORD CANCER TREATED BY RADIOTHERAPY (1950–1964)

Status December 31, 1966

	No. of Patients
Successful:	
Free of evidence of disease treated and any other types of cancer; FLE greater than 0.30	
Alive	47
Died	6
Total	53
Inconclusive:	
Free of evidence of disease treated and any other types of cancer; FLE equal to 0.30 or less	
Alive	52
Died	9
Total	61
Ineffective:	
Alive with recurrence (or with any types of cancer)	9
Died due to disease treated or due to any other types of cancer	7
Total	16
Total number of patients treated	130*

* Excluding 1 lost to follow-up.

DISCUSSION

The main advantages of this new index are summarized as follows:

1. *Inclusion of age, sex and race consideration.* The normal life expectancy is given generally in the national vital statistics according to the age, sex, and race; therefore, the FLE of the individual is automatically adjusted for these factors.

2. *Flexibility for statistical analysis.* The survival rate is a percentage of a group of patients, and the FLE is an index for each individual. The FLE indices obtained for a number of patients are more flexible for statistical analysis, as for instance in the calculation of the frequency distribution of the indices for any subgroups of the patients. Some patterns may be detected as was observed in the example, for instance, which showed that 90 per cent of the recurrences took place within 0.10 of the life expectancy after the time of treatment. Such aspects are not brought out in the survival rate data.

3. *Accumulation of data.* Since the FLE is calculated for each individual, it is not necessary to wait until data have been collected for a large enough group of patients before making any calculations, which is absolutely necessary for calculating the survival rates.

We may conclude that while the survival

rate provides an over-all indication of the percentage of survivals of a patient group with an adequate size, the fractional life expectancy is an additional useful index for analyzing the results of treatment.

SUMMARY

This paper suggests the use of a new index for evaluating the results of treatment by irradiation. The index suggested is the ratio of the duration of survival of a patient after treatment to his normal life expectancy according to his population group. This index is designated as the "fractional life expectancy" (FLE).

The use of the FLE is illustrated by a study of the radiotherapy results of patients with T_1 vocal cord cancer treated during 1950–1964 at the Temple University Hospital.

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I am most grateful to Dr. Robert Robbins for his advice and comments, and for the use of the patients' records in this study.

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The Fiftieth Annual Meeting of the Society will be held at the Hotel Fontainebleau in Miami Beach, Fla., April 7–11, 1968.

EDITORIALS

THE FIFTIETH ANNUAL MEETING OF THE AMERICAN RADIUM SOCIETY

ALL interested physicians are cordially invited to attend the Fiftieth Annual Meeting of the American Radium Society which will be held at the Fontainebleau Hotel, Miami Beach, Florida, April 8, 9, 10, and 11, 1968. The Scientific Program and Schedule of Events, appear elsewhere in this issue of the JOURNAL.

Registration for members and other interested physicians will commence at NOON on Sunday, April 7th, and those planning to attend are urged to apply now for reservations so that they may be accommodated at the Fontainebleau Hotel. There is a nominal registration fee for non-members who are not participating in the program.

The Scientific Program Committee has been overwhelmed with a magnificent selection of abstracts from cities throughout North America. The resultant program reflects the diversified interests of our membership. The theme of this year's Annual Meeting is Therapeutics of Cancer with particular attention to the joint endeavors of surgeon and radiotherapist and the dependence of both on the pathologist. To this end, there will be papers on some aspects of gynecologic cancer, some aspects of head and neck cancer, and dosimetry. There will be a discussion on the pros and cons of hyperbaric oxygenation in radiation therapy.

Three special Panel Symposia are also planned. There will be a panel symposium on pediatric cancer, with invited pediatric surgeon, Lester Martin from Cincinnati, and chemotherapist, Lois Murphy from New York. There will be a panel symposium on the problems of treating esophageal cancer, with the distinguished radiotherapist from Edinburgh, J. G. Pearson, and the distinguished gastrointestinal surgeon, Komei Nakayama from Tokyo joining members of this Society. A panel symposium on prostatic cancer will explore newer trends in therapeutics and will be enhanced by the presence of a biostatistician from The National Institutes of Health, Dr. John C. Bailar, and Dr. Ralph A. Straffon, urologist to the Cleveland Clinic.

The Janeway Lecture will be delivered by Dr. W. Gerald Cosbie of Toronto on, the merits of centralized cancer services to be based on his experiences springing from a lifetime of work with the Ontario Cancer Treatment and Research Foundation.

One aim of the Scientific Program Committee is to encourage discussion and, if members think indicated, controversy! To this end, programs will be received by the members a month ahead of the meeting. Please bring the program with you, study the abstracts, and note that three minute discussions from the podium will be allowed members and invited guests.

The four morning meetings will run from 9:00 A.M. to 1:00 P.M., and the afternoons will be available for other activities.

Dr. Ivor Fix and his Committee on Local Arrangements are offering us not only the salubrious Florida climate, but opportunities for fishing and sight-seeing. The ladies may take boat trips to Ft.

Lauderdale and to Vizcaya, a magnificent estate, and to the seaquarium. In addition, two symphony orchestras and the Cocoanut Grove Playhouse will be in operation. There will be evening receptions on April 8th and April 9th, and on April 10th, the Annual Banquet of the Society. See you in Miami Beach!

John L. Pool, M.D.
President, American Radium Society

755 Park Avenue
New York, New York 10021

HUGH FREDERICK HARE, M.D.
1902–1967

ON THE evening of July 17, 1967 Hugh Frederick Hare, radiologist at the Los Angeles Tumor Institute, passed away suddenly at his home at the age of 65. His active and distinguished career, centered at different times both in the West and in New England, combined the imagination and resourcefulness of the scientific innovator with the warmth and clinical skill and concern of the true physician.

Hugh Hare will be remembered for many things. Underlying his professional career were his deep convictions and understanding of ionizing radiation for the control of malignant disease and his skill and humanity in applying them to the individual patient in his care. These qualities led in 1949 to the fruitful cooperation between his group at the Lahey Clinic in Boston and the physics staff at M.I.T. in investigating the effectiveness of the penetrating X rays from a two million volt Van de

Graaff accelerator combined with rotational administration.

Before he left the Boston area in 1953 for California, the concepts of rotational therapy, the intricately shaped and positioned fields, had been shown to be advantageous and feasible. Moreover, the direct application of low megavolt electrons for the management of extensive superficial malignancies had also been reduced to clinical practice.

The esteem and affection that Hugh Hare inspired in his close associates and patients were also reflected by the professional societies. In 1944 he served as President of the New England Roentgen Ray Society and in 1951 he was President of the American Radium Society. He was also a member of the American Roentgen Ray Society, the Radiological Society of North America, the Rocky Mountain Radiological Society, the Roentgen Society of Colombia (honorary), the New York Academy of Science, and the American Medical Association.

Hugh Hare was born on March 26, 1902, at State College, New Mexico, where his father was a professor. His undergraduate years were spent successively at the New Mexico A and M College (1917–20), Stanford University (1920–21), and Alabama Polytechnic Institute where he received his B.Sc. in 1924. As a fellow at the University of Alabama he taught chemistry and began the medical training which led to his M.D. in 1928 after two years at Harvard Medical School. In this interval he had found time to become a registered pharmacist. He interned for two years at the University of Michigan in internal medicine, and then took up residency in radiology at the Peter Bent Brigham Hospital under Dr. Merrill Sosman from 1930–32. He associated himself with the brilliant Boston surgeon, Dr. Frank Lahey, and was chief radiologist at the Lahey Clinic from 1933–53. He also served as consulting radiologist at the Children's Hospital in Boston 1935–40, Peter Bent Brigham Hospital 1932–53, and the New England Deaconess Hospital 1940–53. His association at M.I.T. was recognized with a research associate appointment.

Dr. Hare moved with his family to California in 1953 and became associated with Drs. William E. Costolow and Orville N. Meland at the Los Angeles Tumor Institute, and he continued his activities in cobalt 60 teletherapy as well as 2 mev. x-ray therapy. In 1957 he initiated the organization of the Southern California Cancer Center, which combines cancer therapy using 2 mev. sources, radium, and isotopes, with a program of cancer research. He organized a night-time industrial radiography program which made use of the 2 mev. Van de Graaff x-ray therapy source to produce funds to help defray the treatment course of patients unable to pay. His clinical investigations with supervoltage x rays and new methods of administration were the subject through the years of scores of papers.

Dr. Hare's home life was a happy one. He was married twice. Louise Henderson, whom he married in 1933, died in 1957. Their two children are Hugh Gerald Hare, now a physician practicing at Falmouth, Mass., and Carolyn Sue, now Mrs. John Coombs, who lives in San Marino, California. There are four grandchildren. In 1959 Dr. Hare married Edna K. Druwing, who had worked with him both at the Lahey Clinic and at M.I.T.

Hugh Hare was a wonderful friend to many people and inspired confidence and affection wherever he went. He was outgoing and helpful, imaginative, gay in spirit, appreciative of his associates and interested in the wellbeing of others. He will indeed be long remembered and admired by the many he worked with and by those he befriended and helped throughout the country. His patients were devoted to him and continue to miss his friendly interest.

John G. Trump, D.Sc.
James F. Nolan, M.D.

THE AMERICAN RADIUM SOCIETY

PRELIMINARY PROGRAM

The following program has been arranged by the Scientific Program Committee for the Fiftieth Annual Meeting of the American Radium Society to be held at the Fontainebleau Hotel, Miami Beach, Florida, April 8–11, 1968.

Sunday, April 7, 1968

9:00 A.M.–3:00 P.M.
Executive Committee Meeting.
Joseph H. Farrow, M.D., Chairman

12:00 NOON–6:00 P.M.
Registration.

Monday, April 8, 1968

8:00 A.M.–4:00 P.M.
Registration.

9:00 A.M.
Opening Ceremonies and Welcome Address, Fiftieth Annual Meeting.
Henry King Sanford, Ph.D.,* President, University of Miami, Coral Gables, Florida.

9:10 A.M.–9:25 A.M.
Presidential Address—The Role of the Specialist in Medicine and Society—John L. Pool, M.D., New York, New York.

FIRST SCIENTIFIC SESSION
Saul B. Gusberg, M.D., Chairman.
Mt. Sinai Hospital, New York, New York.

9:25 A.M.–9:40 A.M.
The Treatment of Ovarian Cancer. D.G.C. Clark, M.D., B. S. Hilaris, M.D.,* and C. Roussis, M.D.,* Memorial Cancer Center, New York, New York.

9:40 A.M.–9:50 A.M.
The Role of Preoperative Radiation Therapy in the Management of Carcinoma of the Ovary. J. M. Vaeth, M.D., Mt. Zion Hospital and Medical Center, San Francisco, California.

9:50 A.M.–10:00 A.M.
Discussion.

10:00 A.M.–10:10 A.M.
The Combination of External Irradiation and Curietherapy Used Preoperatively in Adenocarcinoma of the Endometrium. V. A. Marcial, M.D., and J. M. Tome', M.D.,* Puerto Rico Nuclear Center, San Juan, Puerto Rico.

10:10 A.M.–10:20 A.M.
The Significance of Involvement of the Cervix in Adenocarcinoma of the Uterus. L. Delclos, M.D., G. H. Fletcher, M.D., A. G. Gutierrez, M.D.,* and F. N. Rutledge, M.D., M. D. Anderson Hospital and Tumor Institute at Houston, Houston, Texas.

* *By Invitation.*

10:20 A.M.–10:30 A.M.
Recurrent Endometrial Cancer, Techniques and Results of Treatment. A. Badib, M.D.,* S. S. Kurohara, M.D.,* A. Beitia, M.D.,* J. H. Webster, M.D.,* and J. Graham, M.D., Roswell Park Memorial Institute, Buffalo, New York.

10:30 A.M.–10:45 A.M.
Discussion.

10:45 A.M.–10:55 A.M.
Intermission.

10:55 A.M.–11:05 A.M.
Curative Treatment of Hodgkin's Disease. J. F. Hynes, M.D., Wilmington, Delaware.

11:05 A.M.–11:20 A.M.
The Sites of Recurrence and Extension in Malignant Lymphomas Treated with Radical Radiation Therapy. L. R. Prosnitz, M.D.,* S. Hellman, M.D.,* C. F. von Essen, M.D., and M. M. Kligerman, M.D., Yale University School of Medicine, New Haven, Connecticut.

11:20 A.M.–11:35 A.M.
Discussion.

11:35 A.M.–1:00 P.M.
Panel Symposium: The Treatment of Solid Malignant Tumors in Childhood.
Lemuel Bowden, M.D., Moderator. Memorial Cancer Center, New York, New York.
Surgery:
Lester W. Martin, M.D.,* The Children's Hospital, Cincinnati, Ohio.
Radiation Therapy:
Giulio J. D'Angio, M.D.,* University of Minnesota Hospitals, Minneapolis, Minnesota.
Chemotherapy:
M. Lois Murphy, M.D.,* Memorial Cancer Center, New York, New York.

1:00 P.M.
Adjournment of First Scientific Session.

6:30 P.M.–8:30 P.M.
Reception—Courtesy of the Atomic Energy of Canada, Ltd.

Tuesday, April 9, 1968

7:45 A.M.
First Executive Session. Breakfast Meeting. All members.

* *By Invitation.*

Second Scientific Session
E. Richard King, M.D., Chairman.
Medical College of Virginia, Richmond, Virginia.

9:00 A.M.–9:10 A.M.
Extradural Metastases in Children: A Radiotherapeutic Approach for Rapid Relief of Cord Compression. M. Tefft, M.D.,* and M. D. Schulz, M.D., Children's Hospital Medical Center, Boston, Massachusetts.

9:10 A.M.–9:20 A.M.
Radiation Tolerance of the Thoracic Spinal Cord. F. Buschke, M.D., and T. L. Phillips, M.D.,* University of California, San Francisco, California.

9:20 A.M.–9:30 A.M.
Discussion.

9:30 A.M.–9:45 A.M.
Combined Intra-Arterial Infusion and Radiotherapy for the Treatment of Advanced Cancer of the Head and Neck. R. H. Jesse, M.D., M. D. Anderson Hospital and Tumor Institute at Houston, Houston, Texas.

9:45 A.M.–9:55 A.M.
Treatment of Carcinoma of the Larynx. R. J. Bloor, M.D., and S. M. Kosciolek, M.D.,* Henry Ford Hospital, Detroit, Michigan.

9:55 A.M.–10:10 A.M.
The Natural History and the Radiation Treatment of Lymphosarcomatous Sarcomas of Nasopharynx. J. F. Bohorguez, M.D.,* Michael Reese Hospital, Chicago, Illinois. Sponsored by J. J. Nickson, M.D.

10:10 A.M.–10:20 A.M.
Radiotherapy of Cancer of the Base of the Tongue: 116 Patients Treated in the Years 1952 through 1962. P. W. Scanlon, M.D., E. H. Soule, M.D.,* K. D. Devine, M.D.,* and J. B. McBean, M.D.,* Mayo Clinic and Mayo Foundation, Rochester, Minnesota.

10:20 A.M.–10:35 A.M.
Discussion.

10:35 A.M.–10:40 A.M.
Intermission.

10:40 A.M.–10:50 A.M.
Chemosurgery in the Treatment of Malignancies on the Face. M. W. Eisenstein, M.D.,* Michael Reese Hospital and Medical Center, Chicago, Illinois. Sponsored by J. J. Nickson, M.D.

10:50 A.M.–11:00 A.M.
Interstitial Radiation in the Management of Malignant Disease of the Facial Structures. C. W. Boyer, Jr., M.D.,* T. J. Brickner, Jr., M.D.,* and R. H. Perry, M.D.,* Walter Reed Hospital, Washington, D. C. Sponsored by H. L. Berman, M.D.

11:00 A.M.–11:10 A.M.
Dosimetric Considerations in Cobalt 60 Rotational Therapy for Esophageal Lesions: A Comparison of Transit and Intraluminal Dose Measurement. D. B. Goldenberg, M.D.,* U. V. Gopala Rao, Sc.D.,* and S. Lott, M.D.,* Johns Hopkins Hospital, Baltimore, Maryland.

* By Invitation.

11:10 A.M.–11:25 A.M.
Discussion.

11:25 A.M.–11:30 A.M.
Intermission.

11:30 A.M.–1:00 P.M.
Panel Symposium: The Treatment of Esophageal Cancer.
Vincent P. Collins, M.D., Moderator. Baylor University, Houston, Texas.

11:30 A.M.–11:55 A.M.
Radiation Therapy:
J. G. Pearson, M.D.,* The Royal Infirmary, Edinburgh, Scotland.

11:55 A.M.–12:20 P.M.
Surgery:
Komei Nakayama, M.D,* Tokyo Women's Medical College, Tokyo, Japan.

12:20 P.M.–12:30 P.M.
Radiation Therapy:
W. D. Rider, M.D.,* Princess Margaret Hospital, Toronto, Ontario, Canada.

12:30 P.M.–12:40 P.M.
Combined Therapy:
J. T. Goodner, M.D., Memorial Cancer Center, New York, New York.

12:40 P.M.–1:00 P.M.
Discussion.

1:00 P.M.
Adjournment of Second Scientific Session.

6:30 P.M.–8:30 P.M.
Reception for all members and guests. Host—The Radium Chemical Company.

Wednesday, April 10, 1968

7:45 A.M.
Second Executive Session. Breakfast Meeting. All members.

Third Scientific Session
James F. Nolan, M.D., Chairman.
California Hospital, Los Angeles, California.

9:00 A.M.–9:15 A.M.
Long Time Survivals of Cancer of the Eye and Adjoining Structures Treated with Radiation Therapy. C. L. Martin, M.D., Dallas, Texas.

9:15 A.M.–9:30 A.M.
Radiation Induced Neoplasia Following External Beam Therapy for Children with Retinoblastoma. R. H. Sagerman, M.D., J. R. Cassady, M.D.,* P. Tretter, M.D.,* and R. M. Ellsworth, M.D.,* Columbia-Presbyterian Medical Center, New York, New York.

* By Invitation.

9:30 A.M.–9:40 A.M.
Development of Ultrastructural Radiation Injury. W. R. Hendee, Ph.D.,* M. A. Alders, B.S.,* and C. E. Garciga, M.D., University of Colorado Medical Center, Denver, Colorado.
9:40 A.M.–9:50 A.M.
Cutaneous Reaction to Radiation Therapy. W. S. Maxfield, M.D., and W. P. Coleman, M.D.,* Ochsner Clinic, New Orleans, Louisiana.
9:50 A.M.–10:00 A.M.
Discussion.
10:00 A.M.–10:10 A.M.
Interstitial Implantation of Radioactive Seeds During Thoracotomy for Primary Lung Cancer. U. K. Henschke, M.D., B. S. Hilaris, M.D.,* and J. L. Pool, M.D., Memorial Cancer Center, New York, New York.
10:10 A.M.–10:20 A.M.
Pre and Postirradiation Azygography: Its Value in Determining Surgical Resectability of Pulmonary Carcinoma. C. T. Rinker, M.D.,* and A. W. Templeton, M.D.,* University of Missouri, School of Medicine, Columbia, Missouri.
10:20 A.M.–10:30 A.M.
Discussion.
10:30 A.M.–10:35 A.M.
Intermission.
10:35 A.M.–10:45 A.M.
Clinical Application of Computer Dosimetry in Interstitial Radium Therapy. J. R. Castro, M.D.,* and R. D. Lindberg, M.D.,* M. D. Anderson Hospital and Tumor Institute at Houston, Houston, Texas.
10:45 A.M.–10:55 A.M.
A New Rectal Dosimetry Catheter for Use in Radiotherapy of Carcinoma of the Uterine Cervix. J. J. Sheldon, M.D.,* M. Vuksanovic, M.D., G. J. Wold, M.S.,* and E. A. Fonts, M.D.,* University of Miami, School of Medicine, Miami, Florida.
10:55 A.M.–11:10 A.M.
A Light Analog System for Radiotherapy Planning. G. S. Freedman, M.D.,* and P. N. Goodwin, Ph.D.,* Columbia-Presbyterian Medical Center, New York, New York.
11:10 A.M.–11:25 A.M.
Discussion.
11:25 A.M.–11:40 A.M.
Toxicity Due to Combined Localized Abdominal Radiation and Intravenous Actinomycin Treatment in Dogs. J. P. Concannon, M.D., R. E. Summers, M.S.,* J. King,* and C. Cole,* Allegheny General Hospital, Pittsburgh, Pennsylvania.
11:40 A.M.–11:50 A.M.
The Role of Endolymphatic Isotope Therapy in the Treatment of Malignant Melanoma. I. M. Ariel, M.D., and R. Oropeza, M.D.,* Pack Medical Foundation, New York, New York.
11:50 A.M.–12:00 NOON.
Discussion.
12:00 NOON–12:10 P.M.
Intermission.

12:10 P.M.–1:00 P.M.

The Janeway Lecture

Introduction: Dr. Clifford L. Ash, Ontario Cancer Institute, Toronto, Canada.
"The Centralization of Cancer Services. How Far Should It Go?"
W. Gerald Cosbie, M.D.,* Toronto, Canada.
1:00 P.M.
Adjournment of Third Scientific Session.

1:30 P.M.
Luncheon—Society of Therapeutic Radiologists.

7:00 P.M
Annual Banquet, and presentation of the Janeway Medal.

Thursday, April 11, 1968

Fourth Scientific Session
Fernando G. Bloedorn, M.D., Chairman.
University of Maryland Hospital, Baltimore, Maryland.
9:00 A.M.–9:15 A.M.
Electron Beam Therapy in Head and Neck, and Breast Cancers. N. duV. Tapley, M.D., and G. H. Fletcher, M.D., M. D. Anderson Hospital and Tumor Institute at Houston, Houston, Texas.
9:15 A.M.–9:25 A.M.
The Treatment of Mycosis Fungoides with a High Energy Scanning Electron Beam. M. L. Griem, M.D., F. D. Malkinson, M.D.,* and L. Skaggs, Ph.D.,* University of Chicago, Chicago, Illinois.
9:25 A.M.–9:35 A.M.
Hydroxyurea; A Radiosensitizer in Head and Neck Carcinoma. G. Richards, M.D.,* and R. G. Chambers, M.D., Greater Baltimore Medical Center, Baltimore, Maryland.
9:35 A.M.–9:45 A.M.
Discussion.
9:45 A.M.–10:00 A.M.
The Changing Perspectives in Oxygen Breathing and Radiation Therapy of Cancer. P. Rubin, M.D., C. Poulter, M.B.B.S.,* and R. Quick,* Strong Memorial Hospital, Rochester, New York.
10:00 A.M.–10:15 A.M.
Hyperbaric Oxygen and External Irradiation in the Treatment of Cancer at Various Sites. R. J. R. Johnson, M.B., and R. J. Walton,

* *By Invitation.*

* *By Invitation.*

M.B., Manitoba Cancer Treatment and Research Foundation, Winnipeg, Manitoba, Canada.

10:15 A.M.–10:30 A.M.
Discussion.

10:30 A.M.–10:40 A.M.
Intermission.

10:40 A.M.–10:55 A.M.
Stereotaxic Transsphenoidal Biopsy and Cryosurgery of Pituitary Tumors. R. W. Rand, M.D.,* University of California, Los Angeles, California. Sponsored by J. J. Stein, M.D.

10:55 A.M.–11:10 A.M.
Transantrosphenoidal Hypophysectomy. T. H. Miller, M.D., and H. R. Tollefsen, M.D.,* Memorial Cancer Center, New York, New York.

11:10 A.M.–11:20 A.M.
Discussion.

11:20 A.M.–11:30 A.M.
Response to Radiation Therapy of Osseous Lesions Detected on Radioisotope Bone Scans. S. Baum, M.D.,* J. H. Davenport, M.D.,* and L. Silver, M.D.,* Long Island Jewish Hospital, Jamaica, New York.

* *By Invitation.*

11:30 A.M.–11:40 A.M.
The Radiotherapy of Apparent Primary Mediastinal Seminoma. M. A. Bagshaw, M.D.,* W. T. McLaughlin, M.D.,* J. D. Earle, M.D.,* Stanford University, School of Medicine, Palo Alto, California.

11:40 A.M.–1:00 P.M.
Panel Symposium: The Treatment of Prostatic Cancer.
Juan A. del Regato, M.D., Moderator. The Penrose Cancer Hospital, Colorado Springs, Colorado.
R. A. Straffon, M.D.,* The Cleveland Clinic, Cleveland, Ohio.
J. C. Bailar, M.D.,* National Cancer Institute, Bethesda, Maryland.
F. W. George, III, M.D., U. S. Naval Hospital, San Diego, California.

1:00 P.M.–1:10 P.M.
Third Executive Session.

1:10 P.M.
Adjournment of the Fiftieth Annual Meeting of the American Radium Society.

* *By Invitation.*

NEWS ITEMS

THE ROCKY MOUNTAIN RADIOLOGICAL SOCIETY

At the recent Annual Meeting of the Rocky Mountain Radiological Society, the following new officers for 1968 were elected: *President:* Bertram L. Pear, M.D., Englewood, Colorado; *President-Elect:* Clarence N. Sorensen, M.D., Scottsbluff, Nebraska; *1st Vice-President:* James W. Barber, M.D., Cheyenne, Wyoming; *2nd Vice-President:* Verne G. Latourrette, M.D., Denver, Colorado; and *Historian:* H. Milton Berg, M.D., Bismarck, North Dakota.

The *Secretary-Treasurer* is Robert W. Lackey, M.D., 4200 East Ninth Avenue, Denver, Colorado 80220.

The next Annual Meeting of the Society will be held in Denver at the Brown Palace Hotel on August 15, 16 and 17, 1968.

THE AMERICAN COLLEGE OF RADIOLOGY

Dr. Joseph D. Calhoun, Chairman of the Board of Chancellors, announces that a postconvention travel plan to visit Portugal and Spain by members of The American College of Radiology, following the Chicago meeting February 6 to 10, 1968, has been arranged.

The accommodations and many attractive features of the tour have been specially prepared for The American College of Radiology by Lee Kirkland of Group Travel Services, Inc., and the tour will be personally conducted throughout.

Trans-Atlantic travel will be via TWA and PAN AM and one of the regulations governing use of the special air fare used makes it mandatory that reservation books be closed 30 days prior to departure of the trip. Therefore, reservations must be placed no later than January 10, 1968.

For reservations please contact Lee J. Kirkland, President of Group Travel Services, Inc., 3545 Broadway, Kansas City, Missouri.

COURSE IN MEDICAL USES OF RADIOACTIVE ISOTOPES

A four month, 90 hour course, February 6 to May 28, 1968 in the Medical Uses of Radioactive Isotopes will be offered at the Queens Hospital Center by the Nuclear Medicine Division. The course will consist of weekly five-hour sessions covering lectures, laboratory exercises and clinical management of patients.

For further information please contact Division of Nuclear Medicine, Radioisotope Course, The Long Island Jewish Hospital, Queens Hospital Center Affiliation, 82-68 164th Street, Jamaica, New York 11432.

WORKSHOP IN PEDIATRIC RADIOLOGY

The Second Annual Workshop in Pediatric Radiology will be held at the Children's Mercy Hospital, Kansas City, Missouri, April 22–26, 1968. Guest Professor will be Victor G. Mikity, M.D. Only 10 registrants will be accepted, which permits the curriculum to include participation in daily patient care, special procedures, guest professor lectures, teaching file seminars, and scientific exhibits review.

For additional information please write to Dr. Chas. E. Shopfner, Department of Radiology, Children's Mercy Hospital, 1710 Independence Avenue, Kansas City, Missouri 64106.

COURSE IN NEURORADIOLOGY

The Department of Radiology of the Albert Einstein College of Medicine (with its affiliated hospitals) will present a five day Postgraduate Course in Neuroradiology from May 13 through May 17, 1968. The course is intended for radiologists, neurologists, and neurosurgeons and will be a comprehensive review of the present day concepts of diagnostic neuroradiology. Attention will also be directed towards the practical aspects of specialized diagnostic

procedures. Film interpretation panels will emphasize the approach towards diagnostic problems.

In addition to members of the faculty of the Albert Einstein College of Medicine, the Guest Faculty will include: Dr. James W. D. Bull, Dr. Giovanni di Chiro, Dr. Torgny Greitz, Dr. Irvin I. Kricheff, Dr. Donald McRae, Dr. Harold O. Peterson, Dr. W. Gordon Potts, Dr. Juan M. Taveras, Dr. Ingmar Wickbom, and Dr. Ernest H. Wood.

For further information please write to Mannie M. Schechter, M.D., Program Director, Neuroradiology Postgraduate Course, Albert Einstein College of Medicine, Bronx, New York 10461.

POSTGRADUATE COURSE ON MEGAVOLTAGE THERAPY

A Postgraduate Course on Megavoltage Therapy will be conducted by John Boland, M.D., from May 13 to May 24, 1968, on Monday, Wednesday and Friday, 5 P.M. to 7 P.M.

The course will consist of lectures on the clinical application of cobalt 60 beam, 24 mev. x rays and electron beam, including rotation therapy and small field beam-directed therapy. Particular attention will be paid to dose distribution and calculation, relative biologic efficiency, selection of patients' optimum doses and the management of reactions.

For catalogue and application information please write to the Registrar, The Page and William Black Postgraduate School of Medicine of the Mount Sinai School of Medicine, Fifth Avenue and 100th Street, New York, New York 10029.

NATIONAL BUREAU OF STANDARDS

Calibration of Grenz Rays

To meet the needs for x-ray calibration service for instruments in the soft or Grenz-ray region, a free-air ionization-chamber standard suitable for this part of the x-ray spectrum has been constructed by the NBS Institute for Basic Standards (U. S. Department of Commerce). Construction details together with the results of comparisons of the new chamber with the NBS "low-energy" free-air chamber have previously been given by P. J. Lamperti and H. O. Wyckoff (*J. Res.* NBS, 1965, *69C*, 39–47). Direct comparison of the Grenz-ray chamber has also been made with a free-air chamber at the International Bureau of Weights and Measures (Sèvres, France), and those results will be published shortly.

The radiation qualities for which calibration service is offered in the Grenz-ray region are 10 and 15 kvcp. (=kilovolts constant potential) with a total filtration of 1 mm. Be plus 19 cm. air, having half-value layers of 0.024 and 0.035 mm. Al respectively. A complete listing of NBS x-ray calibration services is contained in NBS Miscellaneous Publication 250, *Calibration and Test Services of the National Bureau of Standards*, available at $1.00 per copy from the Superintendent of Documents, U. S. Government Printing Office, Washington, D. C. 20402.

For further information please write to NBS Office of Technical Information and Publications, U. S. Department of Commerce, Room A 500/101, Washington, D. C. 20234.

BOOK REVIEWS

Books sent for review are acknowledged under: Books Received. This must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interest of our readers as space permits.

PEDIATRIC X-RAY DIAGNOSIS. By John Caffey, A.B., M.D., Visiting Professor of Radiology and Pediatrics, School of Medicine, University of Pittsburgh; Roentgenologist, Children's Hospital, Pittsburgh; Professor Emeritus of Radiology, College of Physicians and Surgeons, Columbia University; Consultant Radiologist, Columbia-Presbyterian Medical Center, New York City; with the collaboration of Frederic N. Silverman, A.B., M.D., Professor of Pediatrics and Radiology, University of Cincinnati College of Medicine; Radiologist and Attending Pediatrician, Children's Hospital, Cincinnati. Fifth edition. Cloth. Pp. 1192, with 1730 illustrations. Price, $39.50. Year Book Medical Publishers, Inc., 35 East Wacker Drive, Chicago, Ill. 60601, 1967.

"There are numerous anatomic variants in the growing skeleton which closely simulate the destructive and productive lesions caused by disease. The diagnostician must be familiar with the sites of these variants, their character and the age of their appearance and disappearance if he is to evaluate films accurately and if he is not to give children diseases which they do not have. Full knowledge of these common variants is much more important and useful than knowledge of the roentgen signs of the diseases themselves."

This quotation, which is taken from the section "The Extremities" of the latest edition of Doctor Caffey's well-known book on Pediatric Roentgenology, epitomizes the author's philosophy, and, it seems to me, the strengths and weaknesses of the book. Doctor Caffey is at his best when addressing himself to the problem of roentgenologic evaluation of growing bones, and particularly of the normal variants which have been the subject of so much interest, and, as he points out, so much confusion and even misdiagnosis.

Throughout the entire chapter on bones, the discussion and the descriptions are lucid and readable, scholarly but not pedantic. One of the best of these descriptions concerns assessment of bone maturation in children; it is typical of Doctor Caffey's erudition and clarity of expression. I would recommend purchase of "Pediatric X-Ray Diagnosis" to anyone interested in the subject if only for this chapter on bones. Of course there are many other chapters and sections which are well worth the reader's time and effort.

The weaknesses of the book are less important. There is a rather discouraging or discouraged approach to many problems, in the discussion of which the author appears to be almost preoccupied by similarity and nonspecificity of roentgenologic findings; this is perhaps most obvious in the chapter on the respiratory tract. The index is not as complete or well organized as it should be—a point of importance in a text which is so widely used as a reference by residents and general radiologists in everyday work.

The bibliography is excellent, yet not exempt from criticism. A list of references is placed at the end of each small section or subsection on related topics, and for the most part this makes easy the task of the reader who wishes to look for individual sources in the reference list. On the other hand, much of the bibliography is not up to date; one list, chosen at random (p. 131), contains 18 references, of which only one, in 1963, is later than 1959. Throughout the book, there are in fact only a few references to the literature of the 5 years preceding the year of publication. Many of the older sources, of course, are of permanent value and one can only be grateful to Doctor Caffey for having sought them out and brought them to our attention. If, however, it is true that medical knowledge is expanding at a rapid rate, one may feel some concern that recent work has received insufficient attention in the preparation of this newest edition of a great book. Use of the bibliography is made easy and pleasant by two points in publishing and editorial policy, which one can only wish were more widely copied: the full title of each article cited in the bibliography is given, and English translations of foreign-language titles are given rather than the original titles.

For the most part, the illustrations are excellent, and show faithfully reproductions of original roentgenograms of high quality. However, there is a tendency to retain some of the older and by present standards inadequate roentgenographic reproductions when better quality examples could likely have been found. In this connection, one notes a tendency to trace or outline on the roentgenograms findings which are not self-evident. This is a practice which I would hope will disappear. If the reproduction does not show the features to which attention is being directed, a tracing should be placed opposite, rather than lines drawn on the roentgenogram itself, since the lines tend to emphasize the inadequacy of the illustrations, and to further obscure the shadows in question.

Enough small lapses and inconsistencies persist in this edition to make one hope that Doctor Caffey, with Doctor Silverman's help, will continue this work and bring out another edition before too long. For example, the author notes that he "discontinued fluoroscopy of the heart because of its limited value, and more important, because of its potential radiation hazards." Yet, in the descriptions of individual normal and abnormal states which follow in the same chapter there are numerous comments about the contribution of fluoroscopy and the fluoroscopic findings. Nor is this edition immune from typographic errors, though they are gratifyingly infrequent.

There is just enough dogmatism in this book to be firm and instructive without being narrow or disturbing. The author is an authority on his subject and quite properly does not hesitate to state his opinion about individual diseases, the diagnostic problems they present, and what part radiology does or should play in their investigation.

Doctor Caffey's solution of the linguistic difficulties which confuse and baffle most of us is surely well known by now, but it continues to be interesting, even diverting. He says "tibias" instead of "tibiae," and by applying this Anglicized (or Americanized?) terminology throughout the text almost consistently, he surmounts or ignores the complexities of Latin or Greek derivations. I say almost consistently, advisedly, because there is no way of writing English well (as Doctor Caffey certainly does), without, in a linguistic sense, being derivative. Thus, the author says "pleuras" instead of "pleurae," but uses a whole constellation of derivative terms to indicate orientation and direction in the body—including laterad, orad, rectad, as well as a few old-fashioned Latin plurals like villi and plicae.

Do publishers of textbooks have any qualms when they faithfully reproduce an author's statement that "space does not permit," and then confront the reader with half a page or more of waste space caused by inefficient layout of cuts and legends? There are enough of these lapses in the 5th Edition of Pediatric X-Ray Diagnosis to cause mild complaint. However, and this is more important, the reproductions and their captions are almost always well composed and apposite to the relevant textual material.

In summary, the latest edition of Doctor Caffey's famous textbook is, like the previous editions, scholarly yet readable, thoughtful but well organized and concise. Buy it.

J. Scott Dunbar, M.D.

Radiological Atlas of Bone Tumours. Volume 1. The Netherlands Committee on Bone Tumours. Cloth. Pp. 267, with many illustrations. Price, $35.00. The Williams & Wilkins Company, 428 E. Preston Street, Baltimore, Md. 21202, 1967.

This book represents the efforts of a study committee on bone tumors, which included radiologists, pathologists, orthopedic and general surgeons. The committee collected sections of bone tumors and data concerning patients from the archives of departments of pathology as well as from referring clinicians treating the patients, who in turn supplied the roentgenograms and the case histories. The experience was also compared with material in the current literature. Sufficient diagnostic documentation was made in 1,569 cases.

The tumors were divided into true neoplasms (malignant and benign tumors) and non-neoplastic lesions of the skeleton. Volume 1 deals exclusively with the experience of 793 malignant lesions of the skeleton. Subsequent volumes will deal with benign tumors and non-neoplastic tumor-like lesions involving the skeleton.

There are excellent introductory chapters with general remarks concerning tumors of the skeleton and general radiographic features for diagnosis of bone tumors. In addition, each tumor is dealt with specifically from the stand-

point of incidence, age, sex, localization, clinical features, radiographic appearance, gross pathology, microscopic pathology, diagnosis, differential diagnosis, prognosis and treatment.

Of the 12 main chapters contained in the book, the first 9 are devoted to osteosarcoma, juxtacortical osteosarcoma, chondrosarcoma, fibrosarcoma, Ewing's sarcoma, myeloma, angiosarcoma and chordoma. Chapter 10 is devoted to the more rare type of malignant tumors including adamantinoma, liposarcoma, and undifferentiated sarcoma. Chapter 11 is devoted to involvement of the bones in malignant disease of the lymphoid and hemopoeitic tissue (Hodgkin's disease, leukemia, acute erythremia and osteomyeloreticulosis). A final chapter is devoted to metastatic tumors.

The book is profusely illustrated with the original roentgenograms presented as log-Etronic positive reproductions. However, in several areas good detail is lacking in the illustrations.

In spite of the reproduction of the roentgenograms as positives, the material is well presented, with excellent descriptive material accompanying each chapter. The atlas will make a useful reference book, not only to the radiologist but also to the clinician and the pathologist.

E. Nicholas Sargent, M.D.

BOOKS RECEIVED

Gynecologic Operations: Indications, Technic and Results. By Otto Käser, M.D., Professor of Obstetrics and Gynecology, University of Frankfurt, Germany; and Franz A. Iklé, M.D., Associate Gynecological Surgeon, Canton Hospital, St. Gallen, Switzerland. English language edition by Albert Davis, M.D., F.R.C.S., Gynecological Surgeon, King's College Hospital Group, London, England, with Renate Marie Davis, M.B., B.S., London, England. Cloth. Pp. 387, with 727 illustrations. Price, $37.50. Grune & Stratton, Inc., 381 Park Avenue South, New York, N. Y. 10016, 1967.

The Spinal Cord. By H. Vakili, M.D., The Roentgen Department, Serafimer Hospital, Stockholm, Sweden. Cloth. Pp. 368, with 263 illustrations. Price, $12.00. Intercontinental Medical Book Corporation, 381 Park Avenue South, New York, N. Y. 10016, 1967.

Second Decennial Review Conference on Cell Tissue and Organ Culture. The Tissue Culture Association Conference held at Bedford, Pa., Sept. 11–15, 1966. Edited by Benton B. Westfall. National Cancer Institute Monograph 26, Sept., 1967. Cloth. Pp. 429, with many illustrations. Price, $4.00. U. S. Department of Health, Education, and Welfare, National Cancer Institute, Bethesda, Md. For sale by the Superintendent of Documents, U. S. Government Printing Office, Washington, D. C. 20402, 1967.

Die intermittierende Kontrastmittelinjektion in das Herz. By Priv-Doz. Dr. Nikolaus Schad, Röntgendiagnostisches Zentralinstitut der Universität Zürich. Paper. Pp. 116, with many illustrations. Price, DM 47.50. Georg Thieme Verlag, Stuttgart. In the U. S. A. and Canada, Intercontinental Medical Book Corporation, 381 Park Avenue South, New York, N. Y. 10016, 1967.

Illustrative Cranial Neuroradiology. By Alfred L. Schmitz, M.D., Associate Clinical Professor of Radiology, University of California at Los Angeles Medical School, Los Angeles; Consultant Neuroradiologist, U. S. Naval Hospital, San Diego; Radiologist, Daniel Freeman Memorial Hospital and Centinela Valley Community Hospital, Inglewood, Calif.; Samuel B. Haveson, M.D., Assistant Clinical Professor of Radiology, University of Southern California Medical School, Los Angeles; Consultant Radiologist, Los Angeles County General Hospital and Harbor General Hospital, Torrance; Radiologist, St. Francis Hospital, Lynwood, Calif.; and Duke Hanna, M.D., Senior Neurosurgeon, Daniel Freeman Memorial Hospital, Inglewood; St. John's Hospital, Santa Monica; Santa Monica Hospital, Santa Monica; and Centinela Valley Community Hospital, Inglewood, Calif. Cloth. Pp. 388, with 269 figures. Price, $31.50. Charles C Thomas, Publisher, 301–327 East Lawrence Avenue, Springfield, Ill. 62703, 1967.

Progress in Clinical Cancer. Volume III. Edited by Irving M. Ariel, M.D., F.A.C.S., Associate Clinical Professor of Surgery and Attending Surgeon New York Medical College, Flower and Fifth Avenue Hospitals; Attending Surgeon and Chief of the Soft Somatic Tissue Tumor Service, Hospital for Joint Diseases; Attending Surgeon, Pack Medical Group, New York, N. Y. Cloth. Pp. 370, with many illustrations. Price, $18.75. Grune & Stratton, Inc., 381 Park Avenue South, New York, N. Y. 10016, 1967.

Error and Variation in Diagnostic Radiology. By Marcus J. Smith, B.S., M.D., F.A.C.R., Radiologist, St. Vincent Hospital, Santa Fe; Espanola Hospital, Espanola; Embudo Presbyterian Hospital, Embudo; Holy Cross Hospital, Taos; Consulting Radiologist, U. S. Public Health Service Indian Hospital; Las Vegas Hospital; St. Anthony's Hospital, Las Vegas, New Mexico. Cloth. Pp. 192, with some illustrations. Price, $8.75. Charles C Thomas, Publisher, 301–327 East Lawrence Avenue, Springfield, Ill. 62703, 1967.

Ultrastructural Changes in Benign and Malig-

nant Epidermal States in Mice After Topical Beta-Radiation. By Kai Setälä, Otto Nyyssönen and Björn Lindroos, Department of Pathology, University of Helsinki. Acta radiologica Supplementum 265. Paper. Pp. 70, with many illustrations. Price, Sw. Kr. 30:–. Acta radiologica, Stockholm 2, Sweden, 1967.

Vascular Response to Vasopressin as Reflected in Angiography: An Experimental Study in the Dog. By Göran Nylander, Department of Roentgendiagnosis and Department of Experimental Surgery, Malmö Allmänna Sjukhus, Malmö, Sweden. Acta radiologica Supplementum 266. Paper. Pp. 80, with many illustrations. Price, Sw. Kr. 35:–. Acta radiologica, Stockholm 2, Sweden, 1967.

Angiography in Renal Tumors: Its Value in Diagnosis and Differential Diagnosis as a Complement to Conventional Methods. By Johan Folin, Roentgendiagnostic Department, University Hospital, Lund, Sweden. Acta radiologica Supplementum 267. Paper. Pp. 96. Price, Sw. Kr. 35:–. Acta radiologica, Stockholm 2, Sweden, 1967.

Carcinoma of the Lung: A Retrospective Study with Special Reference to Pre-Diagnosis Period and Roentgenographic Signs. By Eero Tala, Departments of Radiology, Medicine, and Surgery, University Hospital, Turku, and Paimio Tuberculosis Sanatorium, Paimio, Finland. Acta radiologica Supplementum 268. Paper. Pp. 128, with many illustrations. Price, Sw. Kr. 35:–. Acta radiologica, Stockholm 2, Sweden, 1967.

Iodine 125 as a Radiation Source for Odontological Roentgenology. By Carl O. Henrikson, Department of Roentgenology, School of Dentistry, Karolinska Institutet, Stockholm and Biophysical Laboratory, School of Dentistry, University of Umeå, Umeå, Sweden. Acta radiologica Supplementum 269. Paper. Pp. 90, with some illustrations. Price, Sw. Kr. 35:–. Acta radiologica, Stockholm 2, Sweden, 1967.

Compartments, Pools, and Spaces in Medical Physiology. Proceedings of a Symposium held at the Oak Ridge Institute of Nuclear Studies, and operating unit of Oak Ridge Associated Universities, Oct. 24–27, 1966. Edited by Per-Erik E. Bergner, M.D., and C. C. Lushbaugh, M.D. U. S. Atomic Energy Commission/Division of Technical Information. Paper. Pp. 522, with some illustrations. Price, $3.00. Available as CONF-661010 from Clearinghouse for Federal Scientific and Technical Information, National Bureau of Standards, U. S. Department of Commerce, Springfield, Va. 22151, 1967.

Congrès International sur la Radioprotection dans l'Utilisation Industrielle des Radioéléments, Dec. 13–15, 1965, Paris. Paper. Pp. 174, with some figures. Service Central de Protection contre les Rayonnements Ionisants, Boite Postale No. 35, 78 Le Vesinet, France, 1967.

SOCIETY PROCEEDINGS

MEETINGS OF RADIOLOGICAL SOCIETIES*

UNITED STATES OF AMERICA

AMERICAN ROENTGEN RAY SOCIETY
Secretary, Dr. Ted F. Leigh, Emory University Clinic, Atlanta, Ga. 30322. Annual Meeting: Jung Hotel, New Orleans, La., Oct. 1–4, 1968.

AMERICAN RADIUM SOCIETY
Secretary, Dr. Fernando G. Bloedorn, Division of Radiotherapy, University of Maryland Hosp., Baltimore, Md. 21201. Annual meeting: Hotel Fontainebleau, Miami Beach, Fla., April 7–11, 1968.

RADIOLOGICAL SOCIETY OF NORTH AMERICA
Secretary-Treasurer, Dr. Maurice Doyle Frazer, 1744 South Fifty-eighth St., Lincoln, Neb. Annual meeting: Palmer House, Chicago, Ill., Dec. 1–6, 1968.

AMERICAN COLLEGE OF RADIOLOGY
Executive Director, William C. Stronach, 20 N. Wacker Drive, Chicago 6, Ill. Annual meeting: Drake Hotel, Chicago, Ill., Feb. 6–10, 1968.

SECTION ON RADIOLOGY, AMERICAN MEDICAL ASSOCIATION
Secretary, Dr. Kenneth L. Krabbenhoft, Harper Hospital, Detroit, Mich. 48201. Annual meeting: San Francisco, Calif., June 16–20, 1968.

AMERICAN BOARD OF RADIOLOGY
Secretary, Dr. H. Dabney Kerr. Correspondence should be directed to Kahler Hotel Building, Rochester, Minn.

The Spring 1968 oral examination will be held at the Fontainebleau Hotel, Miami Beach, Florida, June 10–14, inclusive. The deadline for filing applications was December 31, 1967. Candidates eligible for this examination will not be required to take the written examination.

The first written examination will be held the latter half of June 1968 in various centers of the country for all residents having completed 3 years of approved training as of June 30, 1968. Deadline for filing for this examination and the oral examination of December 1968 was December 31, 1967.

AMERICAN ASSOCIATION OF PHYSICISTS IN MEDICINE
Secretary, Leonard Stanton, Hahnemann Medical College, 230 N Broad St., Philadelphia, Pa. 19102. Annual meeting to be announced.

AMERICAN SOCIETY OF THERAPEUTIC RADIOLOGISTS
Secretary, Dr. J. A. del Regato, Penrose Cancer Hospital, Colorado Springs, Colo. 80907.

AMERICAN SOCIETY FOR DIAGNOSTIC ULTRASOUND
Secretary, Dr. Charles C. Grossman, 552 N. Neville St., Pittsburgh, Pa. 15213.

TWELFTH INTERNATIONAL CONGRESS OF RADIOLOGY
President, Dr. Kempo Tsukamoto, 9-1, 4-chome, Angewa, Chiba, Japan. Meeting: Hotel New Otane, Tokyo, Japan, Oct. 6–11, 1969.

NINTH INTER-AMERICAN CONGRESS OF RADIOLOGY
Counselor for the United States, Dr. Juan A. del Regato, Penrose Cancer Hospital, 2215 North Cascade Ave., Colorado Springs, Colo. 80907.
President, Dr. Leandro Zubiaurre, Montevideo, Uruguay. Meeting: Hotel San Rafael, Punta del Este, Uruguay, Dec. 6–12, 1967.

INTER-AMERICAN COLLEGE OF RADIOLOGY
President, Dr. Oscar Soto, H. Urteaga 480, Lima, Perú.

ALABAMA RADIOLOGICAL SOCIETY
Secretary, Dr. Walter Brower, Birmingham, Ala. Meets time and place of Alabama State Medical Association.

ARIZONA RADIOLOGICAL SOCIETY
Secretary-Treasurer, Dr. Robert E. Steyskal, 550 W. Thomas Rd., Phoenix, Ariz. 85013. Two regular meetings a year. Annual meeting at time and place of State Medical Association and interim meeting six months later.

ARKANSAS CHAPTER OF AMERICAN COLLEGE OF RADIOLOGY
Secretary-Treasurer, Dr. William J. Rhinehart, St. Vincent Infirmary, Little Rock, Ark. 72205.

ARKANSAS RADIOLOGICAL SOCIETY
Secretary, Dr. Charles W. Anderson, 1108½ Poplar, Pine Bluff, Ark. Meets every three months and also at time and place of State Medical Association.

ASSOCIATION OF UNIVERSITY RADIOLOGISTS
Secretary-Treasurer, Dr. Harry Z. Mellins, S.U.N.Y. College of Medicine, Brooklyn, New York 11201. Annual Meeting: Ohio State University School of Medicine, Columbus, Ohio, May 9–11, 1968.

ATLANTA RADIOLOGICAL SOCIETY
Secretary, Dr. Donald R. Rooney, Burnt Hickory Road, Marietta, Ga. Meets monthly except during three summer months, on third Tuesday, at the Academy of Medicine, Atlanta, Ga., at 8:00 P.M.

BAVARIAN-AMERICAN RADIOLOGIC SOCIETY
Secretary, Colonel Kurt Harrell, Landstuhl Army Medical Center, Landstuhl, Germany. Meets quarterly.

BLOCKLEY RADIOLOGICAL SOCIETY
Secretary-Treasurer, Dr. R. John Gould, 41 Lombardy Rd., Drexel Hill, Pa. 19026.

BLUEGRASS RADIOLOGICAL SOCIETY
Secretary-Treasurer, Dr. Joe Bernard, Central Baptist Hosp., Lexington, Kentucky 40503. Meets quarterly.

BROOKLYN RADIOLOGICAL SOCIETY
Secretary, Dr. Skottowe DePass, 69-13 Forest Ave., Brooklyn, N. Y. 11227. Meets first Thursday of each month, October through June.

BUFFALO RADIOLOGICAL SOCIETY
Secretary, Dr. Richard Sheehan, 36 Briarlee Drive, Tonawanda, N. Y. Meets second Monday evening each month, October to May inclusive.

CALIFORNIA RADIOLOGICAL SOCIETY
Secretary, Dr. James J. McCort, Santa Clara Valley Med. Ctr., San Jose, Calif. Meets annually during meeting of California Medical Association.

CATAWBA VALLEY RADIOLOGICAL SOCIETY
Secretary, Dr. Emmett R. White, P. O. Box 303, Rutherford College, N. C. 28671. Meets every Friday, Dept. of Radiology, Valdese General Hosp., Valdese, N. C., at 12:00 NOON.

CENTRAL NEW YORK RADIOLOGICAL SOCIETY
Secretary-Treasurer, Dr. Robert A. Bornhurst, State Univ. Hospital, 750 E. Adams St., Syracuse, N. Y. 13210. Meets first Monday each month, October through May.

CENTRAL OHIO RADIOLOGICAL SOCIETY
Secretary, Dr. Ollie E. Southard, 2787 Tudor Rd., Columbus, O. 43209. Meets second Thursday in October, November, January, and March 15 and May 19 at Fort Hayes Hotel, Columbus, Ohio.

CHICAGO ROENTGEN SOCIETY
Secretary-Treasurer, Dr. Fredric D. Lake, 2548 N. Lakeview Ave., Chicago, Ill. 60614. Meets second Thursday of each month, October to April, except December, at the Pick-Congress Hotel at 8:00 P.M.

CLEVELAND RADIOLOGICAL SOCIETY
Secretary-Treasurer, Dr. Theodore J. Castele, 18869 Canyon Rd. Parkview Park, Ohio 44126. Meetings at 7:00 P.M. on fourth Monday of October, November, January, February, March and April.

COLORADO RADIOLOGICAL SOCIETY
Secretary, Dr. Charles E. Seibert, Denver Gen. Hosp., Denver, Colo. 80218. Meets third Friday of each month

*** Secretaries of societies are requested to send timely information promptly to the Editor.**

at Denver Athletic Club from September through May.

Connecticut Valley Radiologic Society
Secretary, Dr. William W. Walthall, Jr., 130 Maple St., Springfield, Mass. Meets in April and October.

Dallas-Fort Worth Radiological Society
Secretary-Treasurer, George E. Plum, 712 N. Washington Ave., Dallas, Tex. 75246. Meets monthly, third Monday, at Southwest International Airport at 6:30 p.m.

Detroit Roentgen Ray and Radium Society
Secretary, Dr. Robert L. Willis, Harper Hospital, Detroit, Mich. 48201. Meets monthly, first Thursday, October through May, at David Whitney House, 1010 Antietam, at 6:30 p.m.

East Bay Radiological Society
Secretary, Dr. Tom H. Piatt, 12 Camino Encinas, Orinda, Calif. 94563. Meets first Thursday each month, Oct. through May, at University Club, Oakland, Calif.

East Tennessee Radiological Society
Secretary-Treasurer, Dr. T. F. Haase, Jr., 205 Medical Arts Building, Knoxville, Tenn. Meets in January and September.

Florida Radiological Society
Secretary, Dr. John C. Jowett, Orlando, Fla. Meets twice annually, in the spring with the annual State Society Meeting and in the fall.

Florida West Coast Radiological Society
Secretary-Treasurer, Dr. Garth R. Drewry, Tampa General Hospital, Tampa, Fla. 33606. Meets in January, March, May, July, September and November.

Georgia Radiological Society
Secretary, Dr. J. L. Clements, Jr., 134 LaGrange St., Newman, Georgia 30263. Meets in spring and fall with Annual State Society Meeting.

Greater Cincinnati Radiological Society
Secretary-Treasurer, Dr. Owen L. Brown, 2421 Auburn Ave., Cincinnati, Ohio 45219.

Greater Louisville Radiological Society
Secretary-Treasurer, Dr. L. D. LeNeave, 315 E. Broadway, Louisville, Ky. 40202. Meets monthly.

Greater Miami Radiological Society
Secretary Treasurer, Dr. Thomas W. Tufts, Broward General Hospital, 1600 S. Andrews Ave., Ft. Lauderdale, Fla. Meets monthly, third Wednesday at 8:00 p.m., at Jackson Memorial Hospital, Miami, Fla.

Greater St. Louis Society of Radiologists
Secretary-Treasurer, Dr. Alexander J. Link, 7215 Maryland, St. Louis, Mo. 63130.

Hawaii Radiological Society
Secretary-Treasurer, Dr. R. K. Wang, P.O. Box 256, Wahiawa, Oahu 96786. Meets third Monday of each month at 7:30 p.m.

Health Physics Society
Secretary, John W. Thomas, Philadelphia, Pa. Annual Meeting: Denver-Hilton Hotel, Denver, Colo., June 16–20, 1968.

Houston Radiological Society
Secretary, Dr. Zoltan Petrany, 1200 Moursond Drive, Houston, Tex. 77025. Meets fourth Monday of each month, except June, July, August and December, at the Doctors' Club, 8:00 p.m., Houston, Tex.

Idaho State Radiological Society
Secretary, Dr. George H. Harris, Bannock Memorial Hospital, Pocatello, Idaho. Meets in the spring and fall.

Illinois Radiological Society
Secretary, Dr. George A. Miller, Carle Hospital Clinic, Urbana, Ill. Meets in the spring and fall.

Indiana Roentgen Society, Inc.
Secretary, Dr. Edwin F. Koch, Jr., 915 University Ave., Muncie, Ind. 47303. Meets first Sunday in May and during fall meeting of Indiana State Medical Association.

Iowa Radiological Society
Secretary, Dr. L. L. Maher, 1419 Woodland Ave., Des Moines, Iowa. Luncheon and business meeting during annual session of Iowa State Medical Society. The scientific section is held in the autumn.

Kansas Radiological Society
Secretary-Treasurer, Dr. Robert C. Lawson, 310 Medical Arts Bldg., 10th and Horne, Topeka, Kan. Meets in spring with State Medical Society and in winter on call.

Kentucky Chapter, American College of Radiology
Secretary-Treasurer, Dr. Ralph C. Quillin, 1221 S. Broadway, Lexington, Ky. 40504. Meets in April and September.

Kings County Radiological Society
Secretary, Dr. Sidney Hendler, 1880 Ocean Ave., Brooklyn 30, N. Y. Meets Kings County Med. Soc. Bldg. monthly on fourth Thursday, October to May, 8:45 p.m.

Knoxville Radiological Society
Secretary, Dr. Clifford L. Walton, Blount Professional Bldg., Knoxville 20, Tenn. Meetings are held the third Monday of every other month at the University of Tennessee Memorial Research Center and Hospital.

Long Island Radiological Society
Secretary, Dr. Samuel Gelband. Meets second Tuesday of the month in February, April, June, October and December.

Los Angeles Radiological Society
Secretary, Dr. Harvey I. Meyers, 2010 Wilshire Blvd., Los Angeles, Calif. 90057. Meets second Wednesday of month in September, November, January, April and June at Los Angeles County Medical Association Building, Los Angeles, Calif.

Louisiana-Texas Gulf Coast Radiological Society
Secretary-Treasurer, Dr. Edward A. Sheldon, 109 Doctors Bldg., Beaumont, Texas 77701.

Maine Radiological Society
Secretary-Treasurer, Dr. Robert A. Bearor, Maine Medical Center, Portland, Maine 04102. Meets in June, September, December and April.

Maryland Radiological Society
Secretary, Dr. Henry Startzman, Medical Arts Building, Baltimore, Md.

Memphis Roentgen Society
Secretary-Treasurer, Dr. Vernon I. Smith, Jr., Suite 203, 1085 Madison Ave., Memphis, Tenn. 38104. Meets first Monday of each month at John Gaston Hospital.

Miami Valley Radiological Society
Secretary, Dr. Darwood B. Hance, Reid Memorial Hospital, Richmond, Indiana. Meets third Thursday of fall, winter and spring months at 7:30 p.m. at Miami Valley Hospital, Dayton, Ohio.

Mid-Hudson Radiological Society
Secretary-Treasurer, Dr. Herbert S. Berlin, Hopewell Junction, N. Y. Meets 7:00 p.m., first Wednesday of each month, September to May.

Milwaukee Roentgen Ray Society
Secretary-Treasurer, Dr. James E. Bell, 8700 W. Wisconsin Ave., Milwaukee, Wis. 53213. Meets monthly on fourth Monday, October through May, at University Club.

Minnesota Radiological Society
Secretary-Treasurer, Dr. Edward A. Peterson, 572 Lowry Medical Arts Bldg., St. Paul, Minn. Meets twice annually, fall and winter.

Mississippi Radiological Society
Secretary-Treasurer, Dr. Dan T. Keel, Jr., 504 Chippewa St., Brookhaven, Miss. Meets third Thursday of each month at the Heidelberg Hotel, Jackson, at 6:00 p.m.

Missouri Radiological Society
Secretary-Treasurer, Dr. Harold B. Rapp, Cape Girardeau, Mo.

Montana Radiological Society
Secretary, Dr. Clark Grimm, Great Falls, Montana. Meets at least once a year.

Nebraska State Radiological Society
Secretary, Dr. Richard Bunting, The Radiologic Center, Nebraska Methodist Hospital, Omaha 31, Neb. Meets third Wednesday of each month at 6 p.m. in Omaha or Lincoln.

Nevada Radiological Society
Secretary, Dr. William G. Arbonies, Department of Radiology, St. Mary's Hospital, Reno, Nev.

New England Roentgen Ray Society
Secretary, Dr. Morris Simon, 330 Brookline Ave., Boston, Mass. 02153. Meets third Friday of each month, October through May, at The Longwood Towers, 20 Chapel Street, Brookline, Mass., at 4:30 p.m.

New Hampshire Roentgen Ray Society
Secretary, Dr. Paul Y. Hasserjian, 1470 Elm St., Manchester, N. H. Meets four to six times yearly.

New Mexico Association of Radiologists
Secretary-Treasurer, Dr. Justin J. Wolfson, Department of Radiology, Bernalillo County-Indian Hospital, Albuquerque, New Mexico.

New Mexico Society of Radiologists
Secretary, Dr. Phil Fox, Albuquerque, New Mexico. Four meetings annually, three held in Albuquerque, N. M., and one held at time and place of New Mexico State Medical Society annual meeting.

New York Roentgen Society
Secretary, Dr. David H. Baker, Babies Hospital, 3975 Broadway, New York, N. Y. 10032. Meets monthly on third Monday at the New York Academy of Medicine at 4:30 P.M. Annual meeting to be announced.

North Carolina Chapter of ACR.
Secretary-Treasurer, Dr. Ira Bell, Hickory, N. C. Annual meeting to be announced.

North Carolina Radiological Society
Secretary, Dr. E. H. Schultz, North Carolina Memorial Hospital, Chapel Hill, N. C. Meets in the spring and fall each year.

North Dakota Radiological Society
Secretary, Dr. A. Ohrt, 408 Medical Arts Bldg., Fargo, N. D. 58102. Meets at time of State Medical Association meeting. Other meetings arranged on call of the President.

North Florida Radiological Society
Secretary, Dr. Charles H. Newell, 800 Miami Road, Jacksonville 7, Fla. Meets quarterly in March, June, September and December.

Northeastern New York Radiological Society
Secretary, Dr. Anthony J. Tabacco, 621 Central Ave., Albany 6, N. Y. Meets in Albany area on second Wednesday of October, November, March and April.

Northern California Radiological Society
Secretary-Treasurer, Ivan D. Siddons, 3701 J. St., Suite 106, Sacramento, Calif. 95816. Meets fourth Monday of Sept., Nov., Jan., March and May at the Sutter Club in Sacramento.

Northwestern Ohio Radiological Society
Secretary, Dr. Vito J. Zupa, Mercy Hospital, Department of Radiology, Toledo, Ohio.

Ohio State Radiological Society
Secretary, Dr. Robert D. Berkebile, Elyria Memorial Hospital, Elyria, Ohio 44035.

Oklahoma State Radiological Society
Secretary, Dr. Donald F. Mauritson, 100 Utica Square Med. Center, Tulsa, Okla. 74114. Meets in January, May and October.

Orange County Radiological Society
Secretary, Dr. George W. Logan, 301 Newport Blvd., Newport Beach, Calif. Meets fourth Tuesday of every month at Orange County Medical Association Building.

Oregon Radiological Society
Secretary-Treasurer, Dr. Irving J. Horowitz, 2311 N.W. Northrup Str., Portland, Ore. 97210. Meets on second Wednesday of month, October through April, at the University Club, Portland, Ore.

Orleans Parish Radiological Society
Secretary, Dr. Joseph V. Schlosser, Charity Hospital, New Orleans 13, La. Meets second Tuesday of each month.

Pacific Northwest Radiological Society
Secretary-Treasurer, Dr. Willis Taylor, 1118 9th Ave., Seattle, Washington. Annual meeting to be announced.

Pennsylvania Radiological Society
Secretary, Dr. T. Frederick Weiland, 619 Ridgeway Ave., Grove City, Pa. 16127. Annual meeting to be announced.

Philadelphia Roentgen Ray Society
Secretary, Dr. C. Jules Rominger, Misericordia Hospital, 54th St. and Cedar Ave., Philadelphia, Pa. 19143. Meets first Thursday of each month at 5 P.M., from October to May in Thompson Hall, College of Physicians.

Pittsburgh Roentgen Society
Secretary, Dr. Edward R. Seitz, 601 Jenkins Bldg., Pittsburgh, Pa. 15222. Meets second Wednesday of month, October through June, at Park Schenley Restaurant.

Radiological Society of Connecticut, Inc.
Secretary-Treasurer. Dr. Henry J. Fox, 10 Washington Ave., Bridgeport, Conn. Meetings are held quarterly.

Radiological Society of Greater Cincinnati
Secretary-Treasurer, Dr. Donald E. Gunderson, 3553 Bayard Dr., Cincinnati, Ohio 45208. Meets first Monday of each month at Cincinnati Academy of Medicine.

Radiological Society of Greater Kansas City
Secretary, Dr. J. Stewart Whitmore, 1010 Rialto Bldg., Kansas City, Mo. Meets last Friday of each month.

Radiological Society of Kansas City
Secretary, Dr. Arthur B. Smith, 800 Argyle Bldg., Kansas City, Mo. Meets third Thursday of each month.

Radiological Society of Louisiana
Secretary, Dr. Lester W. Eavenson, 2700 Napoleon Ave., New Orleans 15, La. Meets semiannually, during Louisiana State Medical Society meeting and 6 months later.

Radiological Society of New Jersey
Secretary, Dr. John W. Marquis, 12 Hawthorne Ave., East Orange, N. J. Meets in Atlantic City at time of State Medical Society meeting and in October or November in Newark, N. J.

Radiological Society of Rhode Island
Secretary-Treasurer, Dr. John M. Vesey, 1196 Elmwood Ave., Cranston, R. I.

Radiological Society of South Dakota
Secretary-Treasurer, Dr. Donald J. Peik, 303 S. Minnesota Ave., Sioux Falls, S. D.

Radiological Society of Southern California
Secretary-Treasurer, Dr. Robert G. Williams, The Santa Barbara Medical Clinic, P.O. Box 1200, Santa Barbara, Calif. 93102. Meets three times a year, usually October, February and May.

Radiological Society of the State of New York
Secretary-Treasurer, Dr. John W. Colgan, 273 Hollywood Ave., Rochester 18, N. Y.

Redwood Empire Radiological Society
Secretary, Dr. Lee F. Titus, 164 W. Napa St., Sonoma, Calif. Meets second Monday every other month.

Richmond County Radiological Society
Secretary, Dr. W. F. Hamilton, Jr., University Hospital, Augusta, Ga. Meets first Thursday of each month at various hospitals.

Rochester Roentgen Ray Society, Rochester, N. Y.
Secretary, Dr. Kenneth E. Robinson, Rochester General Hospital, 1425 Portland Ave., Rochester, N. Y. 14621. Meets at 8:15 P.M. on the last Monday of each month, September through May, at Strong Memorial Hospital.

Rocky Mountain Radiological Society
Secretary-Treasurer, Dr. Robert W. Lackey, 4200 E. Ninth Ave., Denver, Colo. Annual meeting, Brown Palace Hotel, Denver, Colo., Aug. 15–17, 1968.

San Antonio-Military Radiological Society
Secretary, Dr. Hugho F. Elmendorf, Jr., 730 Medical Arts Bldg., San Antonio 5, Tex. Meets third Wednesday of each month in Fort Sam Houston Officer's Club at 6:30 P.M.

San Diego Radiological Society
President-Secretary, Charles R. Henkelmann, 3909 Palm Drive, Bonita, Calif. 92002. Meets first Wednesday of each month at the Town & Country Motel.

San Francisco Radiological Society
Secretary, Dr. H. Joachim Burhenne, Children's Hospital and Adult Medical Center, 3700 California St., San Francisco, Calif. 94119. Meets quarterly at the San Francisco Medical Society, 250 Masonic Ave., San Francisco, Calif. 94118.

Santa Clara County Radiological Society
Secretary, Dr. D. Brendan O'Donnell, 696 E. Santa Clara St., San Jose, Calif. 95112. Meets monthly at the Santa Clara County Medical Association Bldg., 700 Empey Way, San Jose, Calif.

Section on Radiology, California Medical Association
Secretary, Dr. William H. Graham, 630 East Santa Clara St., San Jose, Calif.

Section on Radiology, Medical Society of the District of Columbia
Secretary-Treasurer, Dr. Louis Wener, Cafritz Memorial Hosp., 1310 Southern Ave., S.E., Washington, D. C. 20032. Meets at Medical Society Library, third Wednesday of January, March, May and October at 8:00 P.M.

Section on Radiology, Southern Medical Association
Secretary, Dr. Andrew F. Giesen, Jr., White-Wilson Clinic, Fort Walton Beach, Fla. 32548. Annual meeting to be announced.

Section on Radiology, Texas Medical Association
Secretary, Dr. George F. Crawford, St. Elizabeth Hospital, Beaumont, Tex. Meets annually with the Texas Medical Association.

Shreveport Radiological Club
Secretary, Dr. W. R. Harwell, 608 Travis St., Shreveport, La. Meets monthly on third Wednesday at 7:30 P.M., September to May inclusive.

Society for Pediatric Radiology
Secretary, Dr. John L. Gwinn, Children's Hospital, 4614 Sunset Blvd., Los Angeles 27, Calif. Annual meeting: Jung Hotel, New Orleans, La., Sept. 30, 1968.

Society of Nuclear Medicine
Secretary, Mr. C. Craig Harris, Oak Ridge National Laboratories, Oak Ridge, Tenn. *Administrator*, Mr. Samuel N. Turiel, 430 N. Michigan Ave., Chicago 11, Ill. Annual meeting Chase-Park Plaza Hotel, St. Louis, Mo., June 27–30 1968.

South Bay Radiological Society
Secretary, Dr. Emerson C. Curtis, University Dr., Menlo Park, Calif. 94025. Meets second Wednesday of each month.

South Carolina Radiological Society
Secretary, Dr. George W. Brunson, 1406 Gregg St., Columbia, S. C. Annual meeting (primarily business) in conjunction with the South Carolina Medical Association meeting in May. Annual fall scientific meeting at time and place designated by the president.

South Dakota Radiological Society
Secretary, Dr. Donald J. Peik, 1417 S. Minnesota Ave., Sioux Falls, S. Dak. Meets in spring with State Medical Society and in fall.

Southern California Radiation Therapy Society
Secretary-Treasurer, Dr. Aaron G. Fingerhut, 1000 W. Carson St., Torrance, Calif. 90502. Mets quarterely.

Southern Radiological Conference
Secretary-Treasurer, Dr. Marshall Eskridge, Mobile Infirmary, P.O. Box 4097, Mobile, Ala. 36604. Annual meeting: Grand Hotel, Point Clear, Ala. 36504, Jan, 26–28, 1968.

Southwestern Radiological Society
Secretary, John M. McGuire, 904 Chelsea, El Paso, Tex. Meets last Monday of each month at 6:30 P.M. in the Paso del Norte Hotel.

Tennessee Radiological Society
Secretary-Treasurer, Dr. Marion E. Spurgeon, Memorial Hosp., Clarksville, Tenn. Meets annually at the time and place of the Tennessee State Medical Association meeting.

Texas Radiological Society
Secretary, Dr. Herman C. Sehested, 815 Medical Arts Bldg., Fort Worth 2, Tex. Annual meeting to be announced.

Tri-State Radiological Society
Secretary, Dr. John H. Marchand, Jr., Methodist Hospital, Henderson, Ky. Meets third Wednesday of Oct., Jan., March and May, 8:00 P.M., Elks Club in Evansville, Ind.

University of Michigan Department of Roentgenology Staff Meeting
Meets each Monday evening from September to June, at 7:00 P.M. at University Hospital, Ann Arbor Mich.

Upper Peninsula Radiological Society
Secretary, Dr. A. Gonty, Menominee, Mich. Meets quarterly.

Utah State Radiological Society
Secretary-Treasurer, Dr. Jack J. Davis, Salt Lake Clinic, 333 South Ninth East, Salt Lake City, Utah 84102. Meets fourth Wednesday in January, March, May, September and November at Holy Cross Hospital.

Vermont Radiological Society
Secretary, Dr. John R. Williams, 160 Allen St., Rutland, Vt.

Virginia Radiological Society
Secretary-Treasurer, Dr. K. Kenneth Wallace Jr., Norfolk, Va.

Washington State Radiological Society
Secretary, Dr. Owen Marten, 930 Terry Avenue, Seattle, Wash. Meets quarterly

West Virginia Radiological Society
Secretary, Dr. George G. Green, Morgantown, W. Va. Meets concurrently with Annual Meeting of West Virginia State Medical Society; other meetings arranged by program committee.

Westchester County Radiological Society
Secretary, Dr. Arnold Gerson, Medical Arts Bldg., Mt. Vernon, N. Y. Meets on third Tuesday of January and October and on two other dates.

Wisconsin Radiological Society
Secretary-Treasurer, Harold F. Ibach, 2400 W. Villard Ave., Milwaukee, Wis. 53209. Meets twice a year, May and September.

Wyoming Radiological Society
Secretary, Dr. J. D. Grant, Memorial Hosp., Sheridan, Wyo. Meets in fall with State Medical Society and in spring on call of President.

Cuba, Mexico, Puerto Rico and Central America

Asociación de Radiólogos de Centro America y Panamá. Comprising: Guatemala, El Salvador, Honduras, Nicaragua, Costa Rica and Panamá.
Secretary-General, Dr. Roberto Calderón, Calle Central Oeste No. 218, Managua, Nicaragua, Central America. Meets annually in a rotating manner in the six countries.

Sociedad de Radiología de El Salvador
Secretary, Dr. Julio Astacio, 5a Av. Nte. No. 434, San Salvador, Rep. El Salvador.

Sociedad de Radiología de Guatemala
Secretary, Dr. Carlos E. Escobar, 9ª. Calle A 0-05, Zona 1, Guatemala.

Sociedad de Radiología y Fisioterapía Cubana
Secretary, Dr. Miguel A. García Plasencia, Hospital Curie, 29 y F, Vedado, Habana, Cuba Meets monthly at Curie Hospital.

Sociedad Costarricense de Radiologia
Secretary, Dr. James Fernández Carballo, Apartado VIII, San José, Costa Rica.

Sociedad Mexicana de Radiología, A.C.
Coahuila No. 35, México 7, D. F.
Secretary-General, Dr. Ramón Ruenes.
Meets first Monday of each month.

Asociación Puertorriqueña de Radiología
Secretary, Dr. R. B. Díaz Bonnet, Suite 504, Professional Bldg., Santurce, Puerto Rico.

Sociedad Radiológica Panameña
Secretary, Dr. L. Arrieta Sánchez, Apartado No. 6323, Panamá, R. de P. Meets monthly in a department of radiology of a local hospital chosen at preceding meeting.

Sociedad Radiológica de Puerto Rico
Secretary, Dr. Felipe N. de Jesús, Apt. 9387, Santurce, Puerto Rico. Meets second Thursday of each month at 8:00 P.M. at the Puerto Rico Medical Association Bldg. in San Juan.

British Commonwealth of Nations

Association of Radiologists of the Province of Quebec
Secretary, Dr. R. Robillard, Notre-Dame Hospital, 1560 Sherbrooke St., East, Montreal, Que., Canada. Meets four times a year.

British Institute of Radiology
Honorary Secretary, Dr. G. H. du Boulay, 32 Welbeck St., London, W. 1, England. Meets monthly from October until May. Annual meeting to be announced.

Canadian Association of Physicists, Division of Medical and Biological Physics.
Honorary Secretary-Treasurer, Paul M. Pfalzner, Dept. of Therapeutic Radiology, University of Western Ontario, London, Ont., Canada. Annual meeting to be announced.

Edmonton and District Radiological Society
Secretary, J. D. R. Miller, M.B., University of Alberta Hospital, Edmonton, Alberta, Canada. Meets third Thursday of each month October to May, except December, at various Edmonton Hospitals.

Faculty of Radiologists
Honorary Secretary, Dr. J. N. Pattinson, 47 Lincoln's Inn Fields, London, W.C.2, England. Annual meeting: London, England, June 21–22, 1968.

Faculty of Radiologists, Royal College of Surgeons in Ireland
Registrar, Dr. H. O'Flanagan, F.R.C.P.I., D.P.H., 123 St. Stephens Green. Dublin 2, Ireland.

Section of Radiology of the Royal Society of Medicine (Confined to Medical Members)
Meets third Friday each month at 4:45 P.M. at the Royal

Society of Medicine, 1 Wimpole St., London, W. 1, England.

Canadian Association of Radiologists
Honorary Secretary-Treasurer, Dr. Maurice Dufresne, *Associate Honorary Secretary-Treasurer*, Dr. F. Robert MacDonald, 1555 Summerhill Ave., Montreal 25, Que., Canada. Thirty-first Annual Meeting, Chateau Frontenac, Quebec, Que., March 4–9, 1968.

Montreal Radiological Study Club
Secretary, Dr. Leonard Rosenthall, Montreal General Hospital, Montreal, Que., Canada. Meets first Tuesday evening, October to April.

Section of Radiology, Canadian Medical Association
Secretary, Dr. C. M. Jones, Inglis St., Ext. Halifax, N. S.

Société Canadienne-Française de Radiologie
Secretary General, Dr. Jacques Lespérance, 5415 Boul. L'Assomption, Montreal 26, P. Q., Canada. Meets every third Tuesday from October to April. Annual meeting to be announced.

Toronto Radiological Society
Secretary, Dr. George Wortzman, Toronto General Hosp., Toronto 12, Ont., Canada. Meets second Monday of each month, September through May.

College of Radiologists of Australasia
Honorary Secretary, Dr. T. P. Loneragan, c/o British Medical Agency, 135 Macquarie St., Sydney, N.S.W., Australia.

South America

Asociación Argentina de Radiología
Secretary, Dr. Lidio G. Mosca, Avda. Gral. Paz 151, Córdoba, Argentina. Meetings held monthly.

Ateneo de Radiologia
Secretary, Dr. Victor A. Añaños, Instituto de Radiologia, Santa Fe 3100, Rosario, Argentina. Meets monthly on second and fourth Fridays at 7:00 P.M. in the Hospital Nacional de Centenario, Santa Fe 1300, Rosario.

Colégio Brasileiro de Radiologia
Secretary-General, Dr. Miguel Marıc Céntola, Caixa Postal 5984, São Paulo, Brazil.

Sociedad Argentina de Radiologia
Secretary-General, Dr. Jorge Enrique Barragué, Azeuénaga 888, Buenos Aires. Meetings are held monthly.

Sociedad Boliviana de Radiología
Secretary, Dr. Javier Prada Méndez, Casilla 1182, La Paz, Bolivia. Meets monthly. General assembly once every two years.

Sociedade Brasileira de Radiologia
Secretary, Dr. Armando Rocha Amoédo, Cxa Postal 1532, Rio de Janeiro, Brazil. General Assembly meets every two years in December.

Sociedade Brasileira de Radioterapia
Secretary, Dr. Oscar Rocha von Pfuhl, Av. Brigadeiro Luiz Antonio, 644, São Paulo, Brazil. Meets monthly on second Wednesday at 9:00 P.M. in São Paulo at Av. Brigadeiro Luiz Antonio, 644.

Sociedad Chilena de Radiología
Secretary, Dr. Manuel Concha, Casilla 13426, Santiago, Chile. Meets fourth Friday of each month.

Sociedad Colombiana de Radiologia
Secretary-General, Dr. Armando Uribe, Hospital Militar Central, Apartado aéreo No. 5804, Bogotá, Colombia. Meets last Thursday of each month.

Sociedad Ecuatoriana de Radiología y Fisioterapía
Secretary, Dr. Carlos Palau, Av. Bogotá 206, Guayaquil, Ecuador.

Sociedad Paraguaya de Radiología
Secretary, Dr. Miguel González Addone, 15 de Agosto 322, Asunción, Paraguay.

Sociedad Peruana de Radiologia
Secretary-General, Dra. Ladys del Pino, Instituto de Radiología "Cayetano Heredia" Hospital Arzobispo Loayza, Lima, Perú. Meets monthly except during January, February and March.

Sociedad de Radiologica del Atlantico
Secretary, Dr. Raul Fernandez, Calle 40 #41-110, Baranquilla, Colombia. Society meets monthly at the Instituto de Radiología.

Sociedad de Radiología, Cancerología y Física Médica del Uruguay
Secretary-General, Dr. Ernesto H. Cibils, Av. Agraciada 1464, piso 13, Montevideo, Uruguay.

Sociedade de Radiología de Pernambuco
Secretary, Dr. Manoel Medeiros, Instituto de Radiologia da Faculdade de Medicina da Universidade do Recife, Caixa Postal 505, Pernambuco, Brazil.

Sociedad de Roentgenología y Medicina Nuclear de la Provincia de Córdoba
Secretary-General, Dr. Lucas C. Di Rienzo, Ave. Grl. Paz. 151, Córdoba, Argentina.

Sociedad Venezolana de Radiología
Secretary-General, Dr. Luis F. Muro, Apartado No. 9362 Candelaria, Caracas, Venezuela. Meets monthly, third Friday at Colegio Médico del Distrito Federal, Caracas.

Continental Europe

Österreichische Röntgen-Gesellschaft
President, Dr. Konrad Weiss, Mariannengasse 10, Vienna 9, Austria. Meets second Tuesday of each month in Allgemeine Poliklinik. Annual meeting to be announced.

Société Belge de Radiologie
General Secretary, Prof. Simon Masy, Louvain, Belgium. Meets in February, March, May, June, September, October, November and December.

Société Européenne de Radiologie Pédiatrique
Permanent Secretary, Dr. Jaques Sauvegrain, Hôpital des Enfants-Malades, 149, rue de Sèvres, Paris 15e, France. *General Secretary*, Dr. H. Ludin, Department of Roentgenology, Basler Kinderspital, Basel, Switzerland. Annual meeting to be announced.

Société Française d'Electroradiologie Médicale, and its branches: Société du Sud-Ouest, du Littoral Méditerranéen, du Centre et du Lyonnais, du Nord, de l'Ouest, de l'Est, et d'Alger et d'Afrique du Nord. Central Society meets third Monday of each month, except during July, August and September, rue de Seine 12, Paris, France.
Secretary-General, Dr. Ch. Proux, 9 rue Daru Paris 8e, France.

Československá Společnost pro Roentgenologii a Radiologii
Secretary, Dr. Robert Poch, Praha 12, Srobárova 50, Czechoslovakia. Meets monthly except during July, August and September. Annual general meeting.

Deutsche Röntgengesellschaft
Secretary, Professor Dr. med. H. Lossen, Universitäts-Röntgeninstitut, Lagenbeckstr. 1, Mainz, Germany.

Società Italiana di Radiologia Medica e di Medicina Nucleare
Secretary, Dr. Ettore Conte, Ospedale Mauriziano, Torino, Italy. Meets annually.

Nederlandse Vereniging voor Radiologie
Secretary, Dr. C. B. A. J. Puijlaert, Prof. Dondersstraat 73, Tilburg, Netherlands.

Scandinavian Radiological Society
Secretary-General, Dr. C-E. Unnérus, Hagalund-Tapiola, Havsvindsvägen 5 C., Finland. Annual meeting: Copenhagen, Denmark, 1968.

Sociedad Española de Radiología y Electrología Médicas y Medicina Nuclear
Secretary, Juan Gomez Lopez, Villanueva, 11, Madrid 1. Meets every second Friday of each month, Oct. to June, inclusive, in Madrid. Annual general meeting to be announced.

Schweizerische Gesellschaft für Radiologie und Nuklearmedizin (Société Suisse de Radiologie et de Médecine Nucléaire)
Secretary, Dr. Max Hopf, Effingerstrasse 47, Bern, Switzerland.

Asia

Indian Radiological Association
Secretary, Dr. R. F. Sethna, Navsari Building, Hornby Road. Bombay 1, India.

Indonesian Radiological Society
Secretary, Professor Sjahriar Rasad, Taman Tjut Mutiah I Djakarta, Indonesia

Iranian Radiological Society
Secretary, Dr. Issa Yaghmai, P.O. Box No. 14-1151, Teheran, Iran. The Society meets on the second Saturday of each month.

ABSTRACTS OF RADIOLOGICAL LITERATURE

INDEX TO ABSTRACTS

ROENTGEN DIAGNOSIS

Genitourinary System

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RADIATION THERAPY

Genitourinary System

Hodge, K. E. Combined synchronous voiding ciné-cystourethrography and cystometry in the investigation of vesicoureteral reflux in children. *J. Canad. A. Radiologists*, June, 1967, *19*, 342–348. (From: Henderson General Hospital, Hamilton, Ontario, Canada.)

Vesicoureteral reflux is abnormal and there is general agreement that there is a direct relationship between it and pyelonephritis. Reflux may vary in amount, in its effect upon the upper urinary tract, and in the bladder pressure at which it occurs. The lower the bladder pressure required to produce reflux, the more apt one is to have infected urine delivered back to the kidneys. The author concludes that it is necessary to know whether reflux occurs at high or low pressures as well as to be able to show its appearance on roentgenograms. He has devised a simple method which is useful in determining the bladder pressure at which reflux occurs and at the same time demonstrating the actual reflux. His method does not consider bladder neck outlet problems. He believes that bladder volume and voiding pressure are relatively independent.

The equipment necessary for the procedure is illustrated and tabulated and it is readily available in most hospitals. It is necessary to have fluoroscopy with image intensifier and the author believes that the average radiologist can carry out these examinations without any particular assistance.

Two small catheters are inserted through the urethra into the urinary bladder and all urine is aspirated. The free ends of the catheters are taped to the thighs and are connected to a sterile disposable manometer tubing which is taped to a 90 cm. graduated ruler, and to the infusion bottle which is filled with 500 cc. of 30 per cent cystokon. The infusion bottle is equipped with a sphygmomanometer bulb and air is pumped into the bottle until a steady stream rather than a drip is passing through the tubing into the urinary bladder. The bladder can be filled at the rate of approximately 110 to 120 cc. per minute. This is observed under fluoroscopic control. Bladder filling is continued until the patient voids around the catheters. Filling and emptying of the bladder are observed fluoroscopically and roentgenograms and cine roentgenograms may be taken. The manometer pressure is recorded at the time reflux occurs. The pressure is usually noted by a technician who is watching. The pressure at the commencement of voiding and at the peak in bladder pressures during voiding are also noted.

The assumption is made that the lower the pressure at which reflux occurs, the more severe is the damage to the vesicoureteral junction likely to be. Low pressure is that pressure which normally exists in the urinary bladder. If reflux occurs at this pressure it is likely to be occurring often and reintroducing infected urine into the upper urinary tracts constantly. The author has arbitrarily divided reflux pressures into low pressure groups up to 30 cm. of water, intermediate pressure group refluxing at 30 to 50 cm. of water and high pressure group refluxing at above 50 cm. water level. Classification of reflux into high and low pressure groups accompanied with the roentgenographic appearance of the upper urinary tracts is an excellent guide to treatment of urinary tract infections in childhood.

This article is well illustrated and should be given careful consideration by all radiologists doing any volume of urologic radiology.—*Richard E. Kinzer, M.D.*

Laubenberger, Th., and Jahnecke, J. The percutaneous renal biopsy under radiological control. *German Med. Monthly*, May, 1967, *12*, 206–208. (Address: Dr. Th. Laubenberger, Universitäts-Strahleninstitut, Homburg/Saar, Germany.)

During the end phase of the infusion of a large volume of diluted intravenous contrast medium, maximum nephrographic effect allows good fluoroscopic visualization of the kidneys under image intensification. With the patient prone and the abdomen compressed, an exploring needle is first inserted to measure the depth of the kidney. A Franklin-Silverman needle is then inserted for the renal biopsy.

While blind biopsy is successful in about 80 per cent of attempts, this method under visual control was successful in all but 1 of 97 attempts; adequate tissue was obtained so that no repeat biopsy was necessary. The contrast material did not impair histologic examination.

The usual risks and complications of renal biopsy still exist, but because of the more precise introduction of the needle into the lower pole and the renal hilus, where the larger blood vessels and renal pelvis are located, they can be avoided.—*Mark D. Reiss, M.D.*

Nervous System

Gros, Ch., Wackenheim, A., and Vrousos, C. La thermographie dans les affections du système nerveux. (Thermography in diseases of the nervous system.) *J. de radiol., d'électrol. et de méd nucléaire*, Jan.–Feb., 1967, *48*, 45–47. (From: Chaire d'Electroradiologie, C. H. U. de Strasbourg, France.)

In neurologic and neurosurgical pathology, many diseases show circulatory and neurotrophic disturbances influencing the distribution of thermic energy. Thermographic studies were carried out on 50 patients.

In thrombosis of the internal carotid artery, the authors were able to demonstrate the cold supra-

orbital zone described by Heinz *et al.* and by Wood. The revascularization phase can also be appreciated.

In a case of bilateral carotido-cavernous fistula, the authors were able to follow the postoperative thermic evolution, and also to assess before and after operation the effect of carotid compression on ipsi- and contralateral side.

In cases of medullary compression or syndrome of medullary section, sensory levels exhibit a discrete thermic demarcation line, which is more marked on the dorsal side. In the syndrome of denervation by a peripheral nervous lesion, a cold area is manifest in the corresponding peripheral territory, as for instance in Charcot's disease, Friedreich's disease, and section of a neural trunk.

In the neurovegetative disorders produced by irritation or paralysis of the sympathetic system, thermography can objectivate the cold zone in the involved territory.

All neurologic diseases accompanied by increased vascularity exhibit hyperthermia. Over the skull, the presence of hair prohibits use of thermography. However, frontal lesions (fronto-orbital meningioma, glomic tumors) may be revealed as a hyperthermic area.—*H. P. Lévesque, M.D.*

Oberson, R., and Campiche, R. Etude radioisotopique de la perméabilité des espaces sous-arachnoïdiens périmédullaires, la myéloscintigraphie. (Radioisotopic study of the permeability of the perimedullary subarachnoid spaces: myeloscintigraphy.) *Radiol. clin. et biol.*, 1966, *35*, 208–218. (From: Institut de Radiologie and Départment de Neurochirurgie de l'Hôpital Cantonal Universitaire de Lausanne, Switzerland.)

The term myeloscintigraphy is incorrect in the sense of a direct demonstration of the medulla; in this regard, it cannot be compared to a cerebral scintigraphy (γ-encephalography). It is the exploration of the perimedullary subarachnoid spaces after injection of a radio-element. The permeability of the surrounding meningeal spaces can be ascertained as with the positive contrast myelography and a contrasted picture of the subarachnoid spaces may be obtained by the scintigraphy.

Technique. There is no particular preparation. To avoid subsequent irradiation of the thyroid gland, its affinity for iodine must be blocked by oral administration of a 5 per cent Lugol's solution (15 drops 3 times a day during 6 days). By lumbar puncture, exceptionally by occipital approach, 200 microcuries of radioiodinated human serum albumin are injected into the arachnoid spaces. The patient lies in decubitus position. The first scintigram is obtained 3 to 5 hours after the injection, with the patient in procubitus. The scanning is carried out with conventional equipment in the horizontal plane as close as possible to the spinous processes.

In general, the spontaneous diffusion of the radioisotope in the spaces surrounding the medulla gives a rather homogeneous contrast from the caudad extremity to the great cistern. Sometimes, for an unknown reason, the diffusion is slower; in this case, the patient can be placed in Trendelenburg position (10° to 20°) for 30 to 60 minutes to obtain the desired diffusion.

Results. Thirty-nine cases were investigated with this diagnostic method over a period of 10 months. Side-effects were rare and minor; *e.g.* transient headaches and fever. In 14 cases, the exact localization of an obstacle or a malformation was corroborated by contrast myelography and operation in 7 cases, and by contrast myelography alone in 4 cases. The 3 other cases were verified by follow-up. Two false positive cases were also noted: 1 could be explained by an exaggerated kyphosis at the cervicothoracic junction and the other by a subdural injection. Twenty-one cases proved to be negative and 2 false negative cases were also encountered. In 1 of the latter, a Ewing's tumor invading the sacral canal was not demonstrated even by contrast myelography and in the other, a small tumor of a sacral root was barely visible on contrast myelography.

The lesion site indicated by myeloscintigraphy is lower by 1 or 2 vertebrae compared to the exact level observed at operation. The nature of the obstacle to the diffusion of the radioisotope can rarely be determined. Arachnoiditis produces no typical picture; it can, however, be suspected when abnormal diffusion of the radioisotope is noted; *e.g.*, slow circulation, weak and heterogenous distribution over a long segment of the meningeal cuff. The intra- or extradural location of a compression cannot be determined by myeloscintigraphy, and small-sized lesions cannot be detected. The dynamics, as observed with fluoroscopic examination, are lacking.

In conclusion, myeloscintigraphy does not replace sacculo-radiculography for the demonstration of lumbar disks, or positive contrast myelography for evaluation of the site of a lesion in relation to the dura mater, or to reveal a cirsoid aneurysm. Moreover, it cannot show medullar atrophy as a gazeous myelogram does. However, myeloscintigraphy proves to be a useful screening examination on account of its painless and easy execution and of its innocuity (total resorption of the radioisotope within 24 to 48 hours). It also proves useful for controlling the permeability of the arachnoid spaces during the course of radiotherapy, the differential diagnosis of arachnoiditis, and when the injection of poorly absorbable material or a long and troublesome examination with air should be avoided.—*H. P. Lévesque, M.D.*

Wollin, D. G., Lamon, C. B., Cawley, A. J., and Wortzman, G. The neurotoxic effect of water soluble contrast media in the spinal canal with emphasis on appropriate manage-

ment. *J. Canad. A. Radiologists*, June, 1967, *19*, 296–303. (From: Department of Radiology, Kingston General Hospital, Kingston, Ontario, Canada.)

The clinical courses of 4 patients in whom water soluble contrast medium was inadvertently injected intraspinally and of 1 case with intracranial injection are reported. The reaction began immediately in 4 cases but was delayed for 2 hours in 1 case. Muscle spasms going on to generalized convulsions occurred in all the patients. Hypotension and hyperthermia were not uniformly present. Death occurred in 1 case.

The treatment is described in detail, consisting of general anesthesia, tracheal intubation, artificial and mechanical respiration and the use of curare. Dilantin and luminal were given to reduce excitability but were not effective in preventing or controlling convulsions. Metaraminal was administered for treating hypotension. Hydrocortisone was used routinely but the authors do not believe that it had any dramatic effect. They point out that spinal puncture with drainage of large amounts of spinal fluid has been recommended by others but they did not employ this technique.

The authors carried out experiments on dogs and the results are presented in tabular form. They conclude from the experiments that the reaction is immediate and drastic. They also found that toxicity could be reduced by as much as 800 per cent with pentobarbital sodium anesthesia.

This article is recommended for those persons doing diskography, direct puncture vertebral arteriography and other procedures where the accidental spill of water soluble contrast medium into the spinal canal or intracranial area is a possibility.—*Everett H. Johnston, M.D.*

Skeletal System

Chatelain, A., and Motillon, P. (Dole, France.) Un syndrome d'acro-ostéolyse d'origine professionnelle et de constatation nouvelle en France. (A syndrome of acroosteolysis of occupational origin and its recent observation in France.) *J. de radiol., d'électrol. et de méd. nucléaire*, May, 1967, *48*, 277–280.

Five cases of acro-osteolysis of the bones of the fingers were observed among 441 workers in a polyvinyl chloride factory.

One hundred and three of the 441 workers were directly engaged in cleansing the autoclaves used in polymerization of the vinyl chloride. Fourteen workers in this group presented a clinical syndrome suggesting Raynaud's disease, but without radiologic evidence of bone changes. Five other workers, presented radiologic evidence of bone destruction involving the distal phalanges of the 2nd, 3rd, and 4th fingers of both hands. The toes were not involved.

The clinical symptoms experienced by these patients were primarily those of pain in the involved fingers and an increased sensitivity to cold. There was no evidence of any skin changes, thinning or narrowing of the fingers, or of gangrene.

Routine blood studies failed to reveal any abnormal findings.

The radiologically demonstrable bone destruction or acro-osteolysis, occurred in one of the following patterns:

1. Dissolution of the extreme distal end of the terminal phalanges.
2. Transverse bands of bone dissolution through the distal half of the terminal phalanges, exclusive of the tips.
3. Localized discrete areas of bone destruction, within the phalanges, without surrounding reactive bone changes.

These findings which occurred in 5 out of 103 workers studied in the series present an incidence of slightly below 5 per cent which is considered to be quite high. This calls for measures to improve the techniques and working conditions so as to reduce or eliminate this occupational hazard. Furthermore, the question is raised as to whether the 14 patients with a clinical syndrome simulating Raynaud's disease, but without obvious bone lesions, would not eventually develop such changes if followed up over a period of time.

These are the first such cases observed in France, and reported in the French literature. They bear a resemblance to those reported in the American literature (Ashe, W. F., 1962 and 1964) among workers in Uranium mines, those working with pneumatic drills or carbon oxide.

Reproductions of 6 roentgenograms accompany this article.—*William H. Shehadi, M.D.*

Delahaye, R.-P., Laurent, Henri, and Massoubre, Andrée. Les aspects radiologiques de l'hydatidose osseuse: à propos de 4 observations personnelles. (The radiologic aspects of osseous hydatidosis: report of 4 personal observations.) *J. de radiol., d'électrol. et de méd. nucléaire*, May, 1967, *48*, 269–276. (From: Service d'Electroradiologie de l'H.M.I. Dominique-Larrey, 78-Versailles, France.)

The authors present a comprehensive review of the life cycle of the *Ecchinococcus* tape worm, and of the method of spread of hydatid disease.

The parasite, the *Ecchinococcus granulosus*, a cestode, measures 5–8 mm. in length and usually lives in the intestines of the dog, less commonly the wolf and fox. These serve as intermediary hosts while the sheep, less often the cattle, pig, goat, horse

and camel, are the definitive hosts. Man is an accidental host.

Infestation occurs through contamination from the feces of these animals.

The disease occurs most frequently in South East Europe, North Africa, South America, Australia and the Near East. With increasingly human travel and migration the disease may be seen in countries where it would be least expected and unless its presence is suspected, the diagnosis may be completely missed.

The most frequent organs involved are the liver, the lungs and the kidneys. Bone involvement is rare.

In its natural evolution the hydatid cyst develops a well defined outer membrane sharply separating it from the host organ. Hydatid disease of bone, however, is not circumscribed and the lesion is not encysted, since a definite outer membrane is not formed.

The radiologic appearance is that of an osteolytic bone lesion, with varying degrees of irregular infiltration, often with extensive rarefaction. These changes are striking but their appearance is neither characteristic nor diagnostic. They are usually discovered late in the course of the disease.

The bone changes are irregular and varied presenting the appearance of a malignant lesion. There is irregular, usually extensive, bone destruction, often multilocular, while unilocular lesions are rare. There are no reactive bone changes and no spontaneous healing of the lesion occurs.

Hydatid disease involves and extends through the medulla, with resultant thinning of the cortex and eventually a pathologic fracture with extension into the surrounding soft tissues. The epiphyseal cartilages remain intact, but may be detached and displaced, while the adjacent joints are directly invaded by the disease.

Secondary infection may occur with resultant bone reaction and condensing osteitis, and a so-called ossifying hydatid abscess may develop. When the spine is involved there is accompanying cord compression and nerve root involvement.

Clinical laboratory studies are not helpful. While eosinophilia and a positive Cassoni test are diagnostic when hydatid disease involves other areas of the body, in bone localization of the disease they are often negative.

A high index of suspicion, a careful history, and the presence of secondary deposits in the lungs, as observed on routine chest roentgenograms are helpful in arriving at a diagnosis. A bone biopsy is usually positive.

The authors report on 4 male patients, between the ages of 21 and 42 years: 2 patients with involvement of the right humerus and 2 patients with involvement of the right and left halves of the bony pelvis, respectively.

The *first* patient presented an irregular extensive multilocular lesion involving two-thirds of the shaft of the humerus, a pathologic fracture, soft tissue invasion and a fistula in the soft tissues. A positive diagnosis was made following examination of the discharge from the fistula.

The *second* patient complained of pain in the right arm, presented a well defined eccentric slightly loculated lesion in the mid shaft of the humerus, a circumscribed left parahilar mass, and slightly elevated right diaphragm. At operation a multilocular cystic lesion was found in the shaft of the humerus, without a characteristic limiting membrane. The lesion was curetted and a bone graft made, with eventual good healing.

The *third* patient complained of pain in the left hip, difficulty in walking and recent onset of dysuria. A radiologic examination revealed an extensive multilocular lesion involving the greater portion of the left iliac bone, the left hip and the left sacroiliac joints, and a soft tissue pelvic mass at the level of the left acetabulum. Surgical exploration confirmed the radiologic appearance of extensive bone destruction, cavitation, soft tissue invasion, and the presence of multiple daughter cysts and hydatid fluid.

The *fourth* patient, who was suffering from acute right renal colic, presented on the plain roentgenogram an irregular well defined septated bone defect involving the greater portion of the right iliac bone. Excepting for a positive Cassoni test, all clinical laboratory examinations were negative. The appearance of the lesion in the right iliac bone remained unchanged over a 2 year period, but because of increasing pain an operation was performed which revealed the presence of extensive bone destruction and cavitation with innumerable cysts bathed in a bloody fluid. The postoperative course was uneventful.

A high index of suspicion is essential in trying to establish the diagnosis of hydatid disease of bone; clinical laboratory tests are usually negative or noncontributory (a positive Cassoni test was obtained on the fourth patient), while surgical exploration offers the key to a positive diagnosis, relief of the patient's symptoms and cure of the local lesion.

The diagrams and reproductions of 6 roentgenograms illustrate this interesting article.—*William H. Shehadi, M.D.*

SEVASTIKOGLOU, J. A., and ERIKSSON, I. Familial infantile osteochondrosis deformans tibiae; idiopathic tibia vara: a case report. *Acta orthop. scandinav.*, 1967, *38*, 81–87. (From: Department of Orthopaedic Surgery, University Hospital, Uppsala, Sweden.)

The authors review briefly the history and theories of pathogenesis of idiopathic tibia vera—a deformity apparently secondary to a disturbance of growth and maturation of the medial part of the proximal epiphyseal cartilage. They then report 4 cases in the same sibship.

The patients included identical twin males, age 7 years at diagnosis; sister, age 12 years; and brother, age 10 years. The latter had only roentgenologic evidence of the deformity.

The authors present reproductions of plain roentgenograms of the knees in each patient as well as of the arthrograms of the twins. Although the arthrography disclosed almost normal conditions, the plain roentgenograms in each case showed the typical splaying out of the medial femoral condyle in a beak-like fashion with typical irregularity of the ossification in this portion of the metaphysis.

The authors feel that these cases indicate that this localized growth disturbance is under genetic control. They present a pedigree which suggests a recessive inheritance, but state that until further pedigree data have been collected, no reliable conclusions regarding the mode of transmission can be drawn.—*Donald Hawes, M.D.*

RECHNAGEL, K. Megalodactylism: report of seven cases. *Acta orthop. scandinav.*, 1967, *38*, 57–66. (From: Department of Hand Surgery, Orthopaedic Hospital, Copenhagen, Denmark.)

In this well illustrated article, the author describes the rare disease of megalodactylism which consists of grotesque overgrowth of one or more fingers or toes.

In the 7 cases reported, the overgrowth was present at birth and increased during childhood. The overgrowth usually stops at puberty but can progress into adulthood.

The abnormal growth comprises all tissues, bones as well as soft tissues, and always appears to be associated with considerable thickening or even tumor formation of the median or ulnar nerve and their branches. As a rule only one or a few fingers are affected while the others are entirely normal.

The etiology of the disease is unknown. There are no prophylactic measures. No hereditary features were demonstrated. The microscopic appearances are uncharacteristic.

Of the 7 cases reported, 6 had involvement of the fingers, with the index finger being affected in all 6, the long finger in 4, the thumb in 2, and the ring finger only in 1 case. The little finger was not affected in any case. In the seventh case there was involvement of the second and third toes of the right foot. Three cases were females and 4 males. In all the involvement was unilateral.

In summary, megalodactylism is a rare disease which consists of local giant growth affecting one or more fingers or toes comprising all tissues and often associated with considerable thickening of the nerves supplying the area. The etiology is unknown and the histologic appearances are uncharacteristic. Malignant changes have not been observed. The treatment is restricted to plastic operation, epiphysiodesis, and amputations.—*M. A. Cortese, M.D.*

TAKEUCHI, MASAO. Rubinstein's syndrome in two siblings. *Gunma J. M. Sc.*, March, 1966, *15*, 17–22. (From: Department of Pediatrics, School of Medicine, Gunma University, Maebashi, Japan.)

Rubinstein's syndrome is a rare condition first described in 1963. It consists of children with broad thumbs and toes, peculiar facies and mental retardation.

The author presents the first occurrence of this syndrome in siblings. The proband was a 2½ year old Japanese boy who was extensively studied. His elder brother, who had died at the age of 2 of bronchopneumonia, was studied from hospital records.

The father of the patient had short broad fingers and toes. He had a normal sister, but 3 paternal uncles were mentally retarded. His mother was normal and had had a normal pregnancy. From birth he evidenced poor motor and mental development. His hands were short and wide, the thumbs abnormally wide, and he was unable to appose the fingers. The fore-fingers deviated away from the thumbs, the nails were flat and short. The feet were wide with short second toes and widened fan-shaped first toes. His head was small for his height and weight with a narrow prominent forehead. The hard palate had a high arch. Studies of the blood and urine were normal. Roentgenographic examination revealed posterior flattening of the skull. The carpal ossification centers were small in size for his age, and osseous development was considered poor.

The patient's older brother had had intermittent icterus from the time of birth until his death. He too had a mongolism-like countenance, motor dysfunction, and exhibited the same anomaly of the fingers and toes and was mentally retarded.

The etiology of Rubinstein's syndrome is unknown, but it seems quite likely that this is an hereditary disease. This trait was demonstrated in this and the original report of this syndrome.—*S. A. Kaufman, M.D.*

BLOOD AND LYMPH SYSTEM

CLARKE, C. P., BRANDT, P. W. T., COLE, D. S., and BARRATT-BOYES, B. G. Traumatic rupture of the thoracic aorta: diagnosis and treatment. *Brit. J. Surg.*, May, 1967, *54*, 353–358. (From: Cardiothoracic Surgical Unit, Green Lane Hospital, Auckland, New Zealand.)

Traumatic rupture of the thoracic aorta occurs as a complication of chest injury, and is particularly associated with injuries resulting from sudden deceleration, generally involving the descending aorta just beyond the origin of the left subclavian artery. While such a rupture is usually fatal, approximately 15 per cent of individuals develop a traumatic

aneurysm at the site of the rupture and may live a varying period of time before complete rupture occurs. Since the initial report by Dshanelidze (1923) of a successful repair of traumatic injury of the thoracic aorta, several series have been reported and the authors present their experience with 5 cases of traumatic aneurysm of the descending thoracic aorta.

Roentgenography of the chest always demonstrates widening of the mediastinum and sometimes an associated pleural effusion. This widening may resolve to reveal a localized aortic bulge or may rarely apparently return to normal. Aortography is mandatory both to confirm the diagnosis and to ascertain the site of rupture.

A normal aortogram would suggest that the mediastinal widening was due to bleeding from a vein or small artery and would present an unnecessary thoracotomy. Operation without aortography may result in missing the lesion or overlooking a second rupture. Since most ruptures occur beyond the origin of the left subclavian artery, an upper limb vessel should be used where possible. In cases in which retrograde aortography is not possible, venous aortography may allow diagnosis but will result in poor quality of films. Puncture of the atrial septum, which is theoretically a logical approach, might be considered.

Chronic aneurysms are most often detected as mediastinal masses sometimes calcified on routine chest roentgenograms and the differential diagnosis from other causes of aneurysm depends on the history of deceleration injury, the site of the aneurysm, the age of the patient and the absence of other causes such as syphilis or Marfan's trait.

Acute aneurysms are treacherous and the majority rupture within 3 weeks. However, patients with chronic aneurysm, having survived this initial dangerous period before detection, have a relatively good prognosis. Nevertheless, any false aneurysm is liable to late enlargement and rupture.

The surgical technique for repair of the aneurysms, utilizing a bypass technique, is described.—*James R. Knapp, M.D.*

Fontaine, J. L. Piétri, J., and Babin, S. De l'utilité de l'angiographie sélective d'urgence pour le diagnostic des hémopéritoines; à propos d'un cas de rupture dramatique de l'artère splénique dans une poche de pseudokyste nécrotique du pancréas. (Usefulness of emergency selective angiography in diagnosing peritoneal hemorrhages: report of a case of dramatic rupture of the splenic artery into a pocket of a necrotic pseudocyst of the pancreas.) *Presse méd.*, March 18, 1967, *75*, 655–658. (From: Clinique chirurgicale A, C. H. U., 1, place de l'Hôpital F-67-Strasbourg, France.)

The case reported in detail points out dramatically the importance of selective angiography in the diagnosis of the site of peritoneal hemorrhage, thereby enabling the proper surgical approach and save the life of the patient. Retrograde angiography performed after a futile abdominal surgery for suspected aortic aneurysm, with patient in shock, revealed a hemorrhage pocket in the region of the spleen in the arterial phase and another larger peritoneal pocket medially and superiorly in the venous phase. Immediate ligation of the splenic artery proximal to the site of the rupture (which was caused by a pseudocyst of the body of pancreas) with removal of the spleen and partial pancreatectomy was performed.

This accurate and life saving roentgenographic procedure was not devoid of danger. In fact within a few hours an emergency angioplasty of the right femoral artery was necessitated because an atheromatous plaque (having been dislodged probably by the catheter of the retrograde angiography) had obstructed the artery.

The authors cite from the American literature 7 deaths and 81 serious complications in 11,402 retrograde arteriographies reported. Their experience includes 5 serious complications in 600 arteriographies (1 of which was this case) but with no mortality. Hence, they advise to abstain from retrograde angiography in cases with proven peripheral atherosclerosis (except in such a case as this one, where even though atherosclerosis was strongly suggested, yet the emergency state dictated the procedure).—*Jirair N. Sarian, M.D.*

Ritter, Merrill A., Jacobs, Bernard S., Ecker, Malcolm L., and Pavel, Alan. Varix involving the tibia: a case report. *J. Bone & Joint Surg.*, June, 1967, *49A*, 741–744. (Address: Dr. Merrill A. Ritter, 535 East 70th Street, New York, N. Y. 10021.)

A case of transcortical varix of the anterior aspect of the tibia is reported. There were no generalized varices and the lesion, which was painful and tender, developed following local trauma to the area.

A fluctuant mass which was not pulsatile and which could be obliterated by compression was present on the anterior tibia. Roentgenographic examination revealed a radiolucency through the cortex, without periosteal reaction or cortical thickening. Venous blood was aspirated, and contrast material injected. This revealed a large subcutaneous varicosity communicating through the cortical defect by one large and several smaller channels with the intramedullary system. En bloc excision was performed. Microscopically, multiple endothelium lined vessels filled with blood were seen. There was a very delicate supporting stroma. Some bone resorption was noted.

Studies of the vascular anatomy of the tibia have disclosed large tubelike transcortical vessels com-

posed solely of endothelium. It is possible that under the influence of local trauma these veins may enlarge and develop into varices.—*Mark D. Reiss, M.D.*

Tinguely, H., Bopp, P., and Wettstein, P. Association phéochromocytome-hyperplasie fibro-musculaire: coïncidence ou entité nosologique; rapport d'un cas. (Association of pheochromocytoma and fibro-muscular hyperplasia: coincidence or nosologic entity: report of a case.) *Radiol. clin et biol.*, 1966, *35*, 311–315. (From: Institut de radiologie and Institut de cardiologie, Hôpital cantonal universitaire, Genève, Switzerland.)

The authors report a case of pheocrhomocytoma diagnosed and localized by retrograde (femoral) angiography. A vascularized round tumor of about 5 cm. in diameter was noted immediately above the upper pole of the right kidney. Godrooned or notched contour of the right renal and of the inferior mesenteric arteries was demonstrated indicative of fibromuscular hyperplasia of their walls. These roentgen findings were extensive and not transient (thus spasm could be ruled out).

The authors believe with others that this is a systemic vascular dysplasia and not limited only to the renal arteries. It remains to be proven, statistically, if pheochromocytoma and vascular fibromuscular hyperplasia are associated with significant implication as to the treatment of arterial hypertension.

Pathogenetic association of fibro-muscular hyperplasia and pheochromocytoma needs to be investigated systematically.—*Jirair N. Sarian, M.D.*

Ekwueme, C. O., and Anomah, Ngu, V. Inferior vena caval obstruction complicating vertebral column disease. *Brit. J. Surg.*, July, 1967, *54*, 587–590. (From: Department of Surgery, University of Ibadan, Ibadan, Nigeria, Africa.)

Two cases are reported in which inferior vena caval obstruction was associated with lesions in the vertebral column at the level of the obstruction. Both patients were young adults with healed inflammatory lesions in the spine—one proven tuberculosis and the other probably tuberculosis.

In the first case, a 30 year old male, roentgenograms of the lumbar spine showed collapse of the third and fourth lumbar vertebrae, with considerable sclerosis. A left femoral venogram revealed complete obstruction of the inferior vena cava at its origin near the collapsed fourth lumbar vertebra.

The second case, a 26 year old man, showed sclerosis of the first and second lumbar vertebrae on the roentgenograms. A venogram on this patient disclosed a complete block of the inferior vena cava at the level of the first and second lumbar intervertebral disk space.

From the close position of the inferior vena cava to the spine, the obstruction in these 2 cases appears to have been caused by direct compression of the vein by fibrosis secondary to the healing of the vertebral disease.—*John H. Harris, M.D.*

Amsler, Fred, R., and Wilber, Martin C. Intraosseous vertebral venography as a diagnostic aid in evaluating intervertebral-disc disease of the lumbar spine. *J. Bone & Joint Surg.*, June, 1967, *49A*, 703–712. (From: The Orthopedic Department, United States Naval Hospital, Philadelphia, Pa.)

The authors describe intraosseous vertebral venography and its usefullness as demonstrated in 42 patients. These patients were also studied with myelography and surgical exploration.

The vertebral veins are divided into an external and an internal plexus which communicate through intervertebral veins and tortuous veins between posterior vertebral arches. The internal plexus consists of 2 anterior and 2 posterior longitudinal channels separated by the dura. These anastomose freely to form a venous ring around each vertebra. The intervertebral veins terminate in the vertebral, intercostal, ascending lumbar and lateral sacral veins. The veins are thin-walled, distensible and valveless. They are extracavitary and thus receive intracavitary blood readily when the abdomen is subjected to mechanical compression. When the veins are filled with contrast material via intraosseous injection in the lumbosacral region, they have a symmetric ladder-like appearance, the rungs of which represent the intervertebral veins. Failure to fill the intervertebral veins is abnormal and suggests a space-occupying lesion.

The technique utilizes mechanical compression of the abdomen and consists of carefully drilling a $1\frac{1}{2}$ inch Osgood needle, No. 18, into the selected spinous process. The needle must lie in the cancellous portion of the spinous process. One cc. of 60 per cent renografin is injected as a test dose followed by 5 cc. of 1 per cent lidocaine. Thirty cc. of 60 per cent renografin is then injected in 3 to 5 seconds and a film exposed with the last 5 cc. A second injection of 20 cc. and a second exposure then follows. The tube should be tilted 5 to 10 degrees toward the sacrum to demonstrate the lumbosacral interspace.

The venogram localized disk disease in 35 of 42 patients. Of the 7 remaining patients, there were 3 false negatives, 1 false positive, 1 in which the venogram demonstrated one disk but another was also present and in 2 cases the venogram localized the defect on the side opposite the one demonstrated by surgical exploration.

The authors state that laterally placed lesions are

better demonstrated with venography and central lesions with myelography. It is felt that the technical and interpretative problems with this study would require its performance by one person rather continuously in any one institution.—*Major James R. Stevenson, MC USA*

Halliday, Peter. Intra-osseous phlebography of the lower limb. *Brit. J. Surg.*, April, 1967, *54*, 248–257. (From: Department of Surgery, University of Sydney, and the Royal Prince Alfred Hospital, Sydney, Australia.)

The author describes a technique of intraosseous phlebography of the lower limb designed to demonstrate incompetent perforating veins and to define changes in the deep veins of patients with venous disorders of the lower limb.

One hundred and fifty-five patients were divided into 3 groups: postphlebitic patients; patients with primary varicose veins; and normal patients examined to exclude venous disorders.

A bonemarrow needle with plastic extension tubing was inserted into the lateral malleolus, 2 cm. above the tip to a depth of 1 cm. When the examination was done utilizing local anesthesia, 1 cc. of Xylocaine was then injected followed by 5–10 ml. of 30 per cent urografin, while a sphygmomanometer cuff was inflated to 100 mm. Hg on the thigh. Then 40 ml. of 30 per cent urografin was injected in 30–40 seconds. Anteroposterior and lateral roentgenograms were obtained while the injection was taking place.

Contrast material flows immediately to the deep veins and the short saphenous vein but the long saphenous vein fills very faintly or not at all. The pathologic veins were divided into 2 groups: incompetent perforating veins subject to surgical treatment; and those not subject to surgical treatment, such as soleal sinusoids and fine multiple veins. Incompetent perforating veins were found in 90 per cent of patients with the postphlebitis syndrome and over one-half were medial perforating veins, one-third posterior perforating veins, and one-sixth lateral perforating veins. In patients with primary varicose veins, 50 per cent had incompetent perforating veins and in normal patients none were demonstrated.

Deep vein abnormalities were found in all but 2 of 130 postphlebitic patients. The abnormalities consisted of occlusion, 'disorganization', and recanalization. The occlusion was usually localized to the distal popliteal vein, proximal to the junction of the soleal sinusoids and the posterior tibial vein. Tortuous collateral veins, absence of valves and irregularity of the wall in the area of the filling defect help distinguish occlusion from failure of contrast medium to opacify a segment of the vein. Recanalization, partial or complete, was characterized by no valves, fluffy outlines, dilatation and diminished intensity.

In patients with primary varicose veins, occlusion and recanalization were present but less frequent and less severe.

It was felt that, in addition to establishing the clinical diagnosis, the examination demonstrated the distribution of incompetent perforating veins thus determining the extent of the surgical procedure. In a small group of patients, a subfascial ligation was avoided when abnormalities in the deep veins were demonstrated in the absence of incompetent perforating veins.—*Major James R. Stevenson, MC USA*

Davidson, J. W., Clarke, E. A., and Walker, D. Radiographic appearances in chromolymphadenography. *J. Canad. A. Radiologists*, June, 1967, *19*, 316–321. (From: Department of Diagnostic Radiology, Princess Margaret Hospital, Toronto, Ontario, Canada.)

Chromolymphadenography, whereby chlorophyll is added to ultrafluid lipiodol for diagnostic lymphography, is a successful method of coloring lymphatic structures green. The green color visible at operation aids in the identification of the lymph nodes visualized on preoperative lymphangiograms. Ordinarily, the lymph nodes are best demonstrated 24 hours after the injection of plain ultrafluid lipiodol. With chlorophyll added, however, there is a marked stasis of the contrast medium in the lymph vessels. In 35 cases of chromolymphadenography marked stasis was noted at 24 hours to 1 month following the procedure and lymph node swelling was noted in 6 cases. In only 1 case of plain lipiodol lymphangiography was a minimal stasis noted at 24 hours.

The radiographic appearance is dilatation of varying degrees in numerous afferent channels continuous with the sinus of the lymph node. There is a paucity of efferent vessel filling. Collateral vessels and lymph nodes not usually visualized in the plain lipiodol studies are seen. Marked dilatation of the marginal sinuses and adjacent lymph vessels may occur simulating small lymphocysts. The lymph nodes are often larger in size with poorer marginal definition and loss of normal reticular pattern. This appearance may be confused with metastatic disease.

The authors compared their study with two others previously published and the results are similar. They believe that these findings indicate a definite reaction to chlorophyll and that the edema of green-stained lymph nodes removed at surgery would confirm this.

It is concluded that the disadvantages of the chlorophyll type of lymphadenography outweigh the advantages.—*Everett H. Johnston, M.D.*

RADIATION THERAPY

DAVIDOFF, LEO M. Some considerations in the therapy of pineal tumors; Rudolf Virchow lecture. *Bull. N. Y. Acad. Med.* July, 1967, *43*, 538–562.

The author reviews historically the pathophysiology of the pineal gland and its tumors. Also, he discusses the anatomic location of the tumor as it relates to the production of: (1) obstructive hydrocephalus, (2) interference with the function of the quadrigeminal plate and midbrain, (3) interference with function in the hypothalamic-pituitary lesion, and (4) endocrine manifestations secondary to depression or hyperactivity of the pineal gland. The need for accurate diagnosis based upon ventriculography is stressed.

In reviewing the literature he points out the high mortality and general futility associated with the radical surgical treatment of pineal tumors as the primary means of therapy. In addition, he presents his own case material which has been treated by means of a surgical decompression utilizing some form of shunting procedure. A detailed discussion of various surgical shunts follows.

The need for adequate radiation therapy to the tumor following the surgical procedure is emphasized. Of 11 cases treated in this combined manner, 9 are alive and well 9–24 years following treatment.—*Donald S. Faust, M.D.*

HEUSCHELE, R., and LAMPE, I. Pituitary irradiation for Cushing's syndrome. *Radiol. clin. et biol.*, 1967, *36*, 27–31. (From: The Department of Radiology [Alice Crocker Lloyd Radiation Therapy Center] University of Michigan, Ann Arbor, Mich.)

In 16 patients with Cushing's syndrome due to adrenal hyperplasia produced by excessive secretion of ACTH, pituitary irradiation (4,000 r in 4 or $4\frac{1}{2}$ weeks) was followed by complete remission of all the manifestations of the syndrome in 10 patients (63 per cent). Five patients had initial improvement but the manifestations recurred; thus they were considered failures (31 per cent). One patient had no response. The prognosis was more favorable for the younger patients.

The average age of the 10 patients with complete remission was 26.3 years (range 16 to 47) in contrast to 45.3 years (range 37 to 52) for the 6 failures. Ample time must be allowed for the development of a satisfactory remission, often in excess of 6 months. The average time for clinical remission was 7.4 months.

The delayed onset of remission may operate against employing this method of treatment in patients with markedly severe manifestations of Cushing's syndrome. A remission rate of approximately 50 per cent in Cushing's syndrome due to adrenal hyperplasia produced by excessive secretion of ACTH can be expected on the basis of the authors' series and the findings reported in the literature.—*A. D. Belcher, M. D.*

MICELI, R., CALABRESE, U., and MARANI, A. Localizzazioni scheletriche nel linfogranuloma maligno. (Skeletal localization in malignant lymphogranuloma.) *Radiobiologia, radioterapia e fisica med.*, Jan.–Feb., 1967, *22*, 11–32. (From: Istituti di Radiologia e del Radio, Università di Bologna, and Istituto di Radiologia e Terapia Fisica dell'Ospedale Maggiore di Bologna, Italy.)

Between 1930 and 1967 a total of 304 cases of Hodgkin's disease were treated at the Istituto del Radio of Bologna. Twenty nine cases presented skeletal involvement.

The age varied from 8 to 65 years, the fourth decade showing the highest incidence. Of the 29 patients, 19 were males.

In 12 cases there was only a single skeletal localization, while in the remaining 17 the skeletal involvement was multiple. The most frequent localizations were to the lumbar spine (10 cases), and the dorsal spine (7 cases).

The pathologic process in 21 cases was of the osteolytic type. In only 6 cases was the form of a mixed type, osteolytic and osteoblastic.

Radiotherapy was the treatment of choice with total doses varying from a minimum of 850–900 rads to a maximum of 5,000–6,000 rads. The results were satisfactory but the beneficial effects were of short duration.—*A. F. Govoni, M.D.*

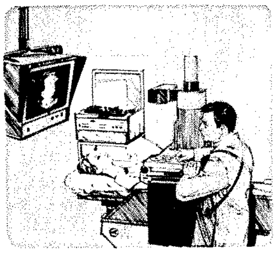
PERTTALA, Y., HOLSTI, L. R., and RISSANEN, P. M. Histiocytosis X (reticulo-endotheliosis). *Radiol. clin. et biol.*, 1967, *36*, 53–64. (From: The Radiotherapy Clinic, University Central Hospital, Helsinki, Finland.)

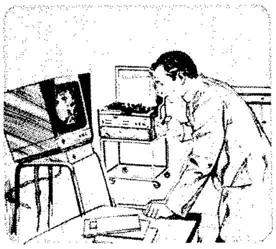
Eight cases of histiocytosis X (4 adults and 4 children) were examined at the Radiotherapy Clinic from 1950 to 1965.

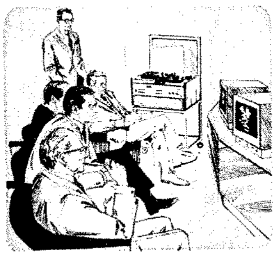
The clinical features, roentgenologic findings, and the treatment of these cases are described. Six of them were males and 2 females. The age range was 3 months to 53 years. The follow-up time was 1–16 years.

The course of the disease was followed by clinical roentgenologic examinations performed at regular intervals.

A table presenting the clinical and roentgenologic findings in these 8 cases is presented.—*John H. Harris, M.D.*







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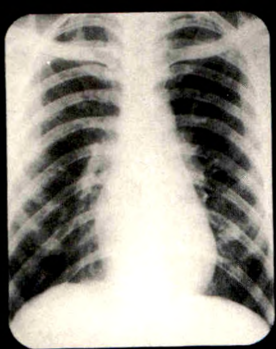

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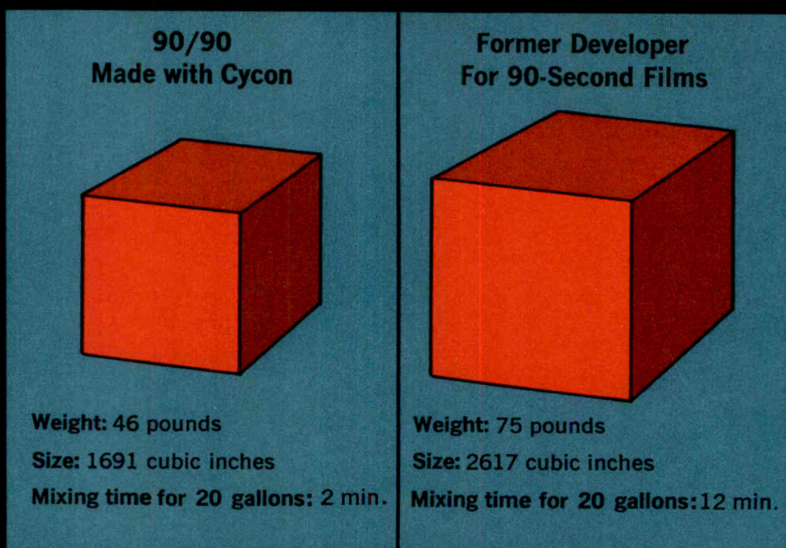

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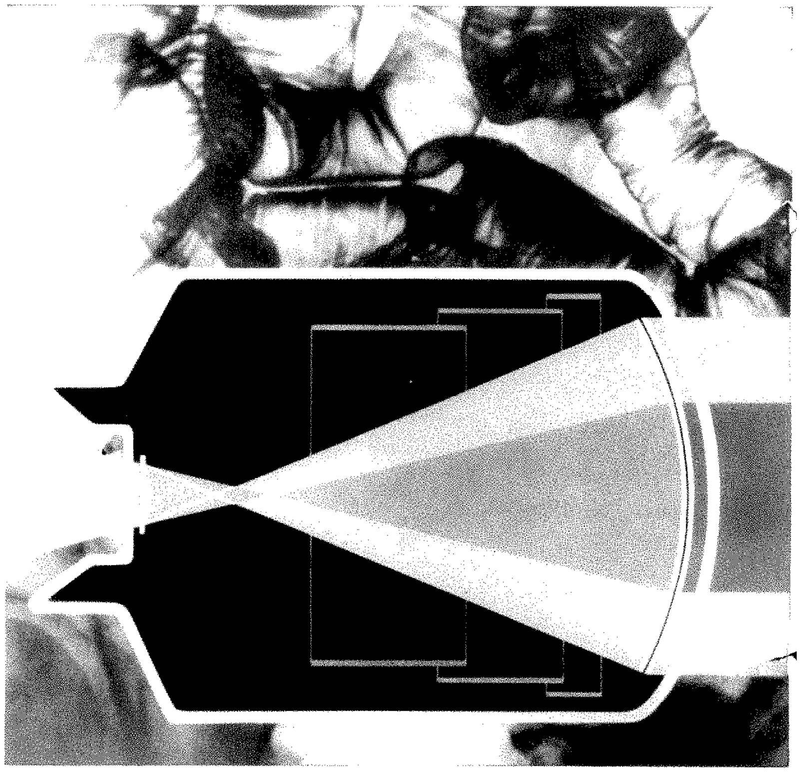

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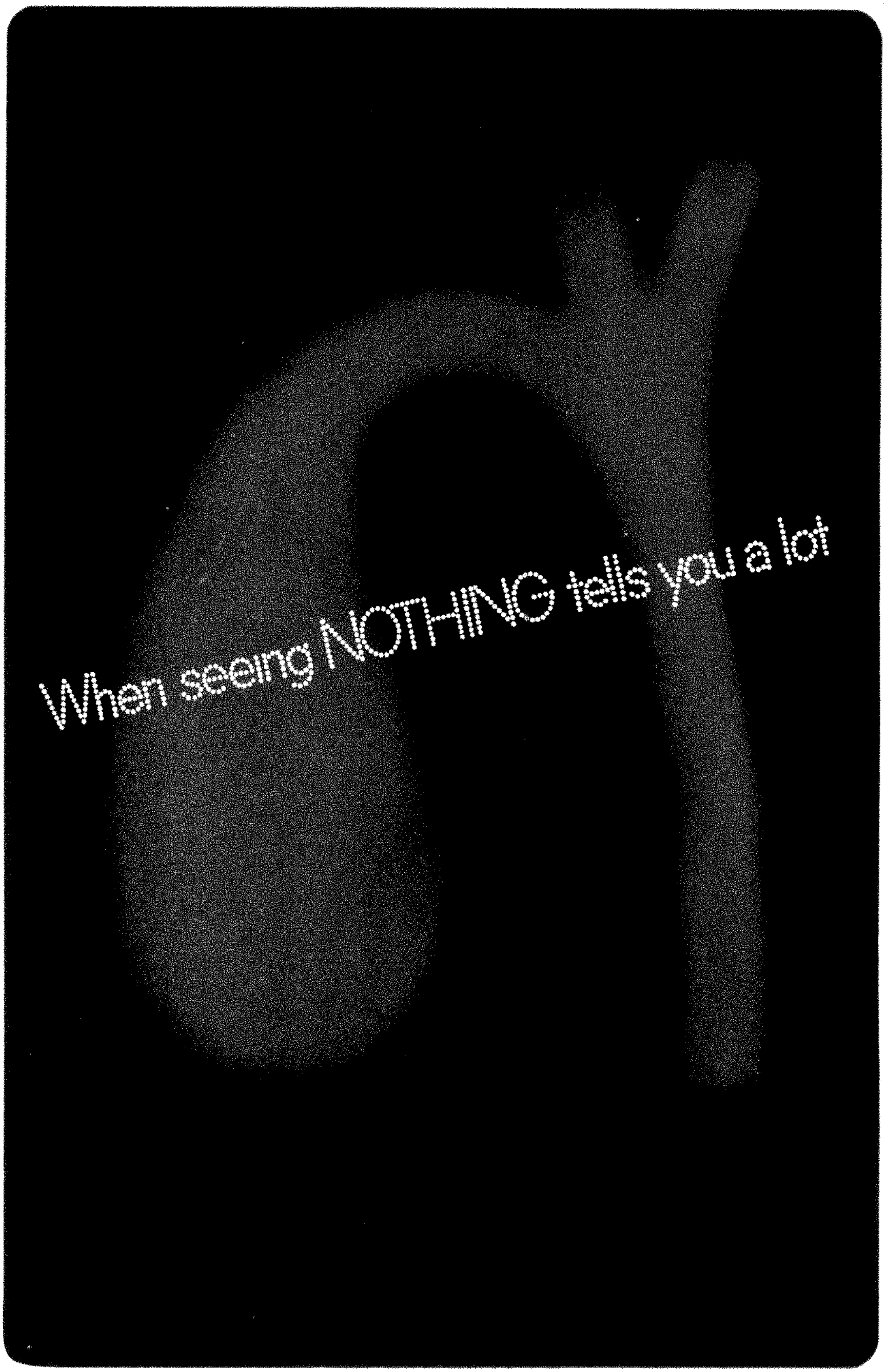
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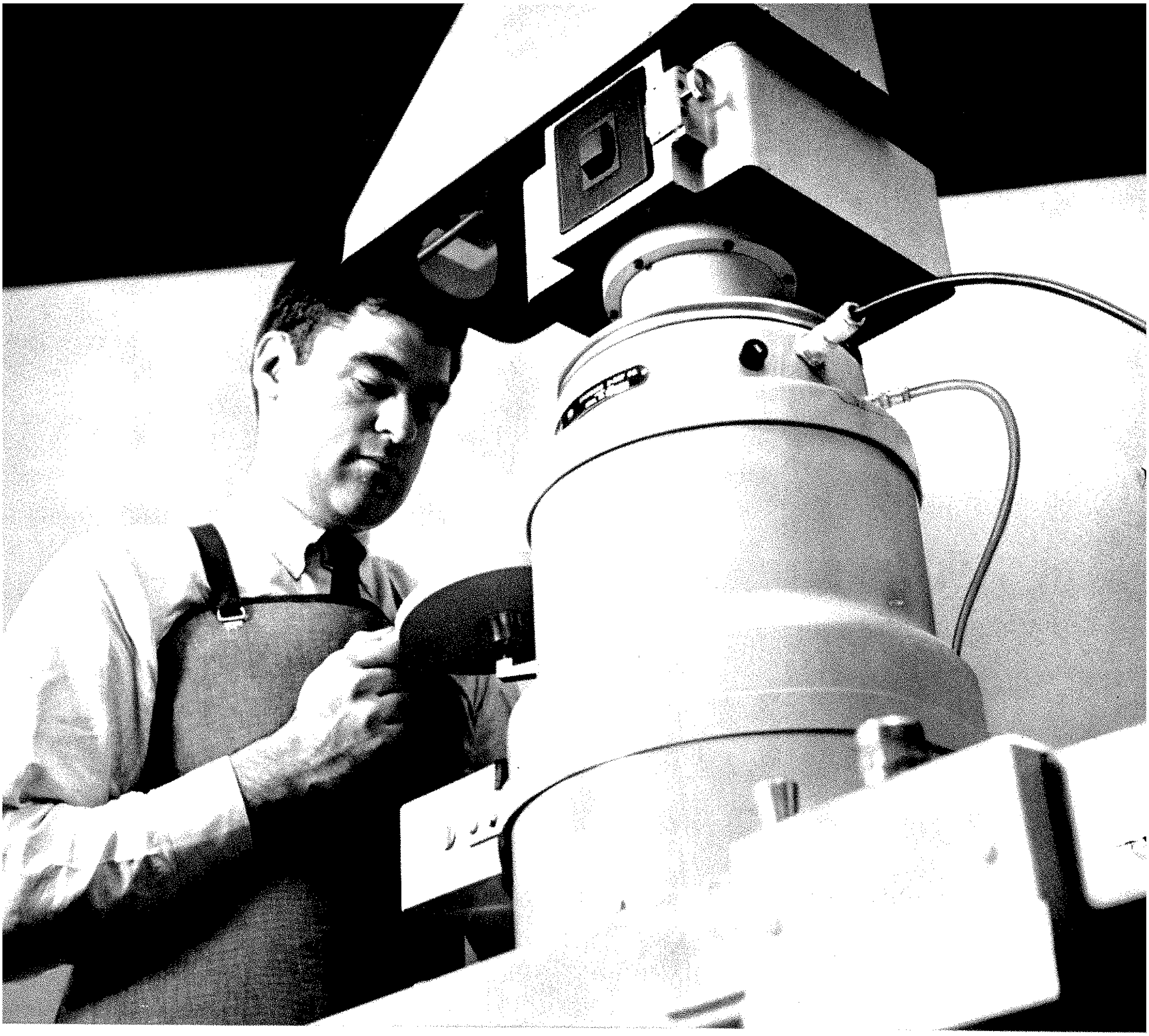

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Most important, the Ultiscope Image Intensifier is the result of Standard's 53-year old tradition of making reliable, superior-quality X-ray equipment. It's built by craftsmen who put an extra amount of care and precision into every one of the jobs they do.

STX-8-212

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Shedding a conventional 12½ lb. leaded x-ray apron and donning our new light one is just like emptying your pockets of 1 silver dollar, 2 half dollars, 87 quarters, 38 dimes, 99 nickels, 181 pennies, a ball point pen, 1 pocket knife and 4 keys.

But despite this lower weight, you lose no protection with this apron. Our new Lite-Gard apron fully provides the required 0.5 mm lead equivalent protection at 80 KV. Yet it actually weighs up to 4 lbs. less than conventional x-ray aprons.

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But you need not wait for said demonstration: details will follow your request for file MA-32.

SQUIBB

a research concept in contrast visualization

for better definition of disease: documenting differences between contrast agents

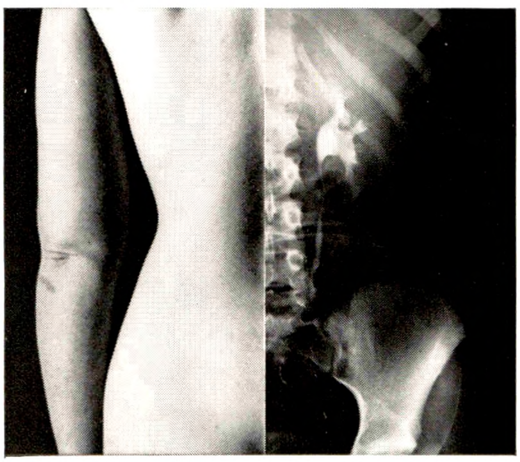
No. 1 in a series:

Renografin-60 (meglumine diatrizoate injection) preferred in a study of pyelographies of 2,234 patients.

In a new large scale study,[1] "...to determine which medium would produce adequate visualization of the urinary tract with the fewest toxic effects on the patient," Macht *et al.* have compared Renografin-60 with 2 other contrast agents.

Data were analyzed in 2,234 unselected (consecutive) patients, according to age, sex, and general disease group for the study population as a whole. The first 683 patients received 50% diatrizoate sodium solution, the next 921 patients received Renografin-60, and the final 630 patients received 66.8% sodium iothalamate solution.[1]

criteria for quality and comparative safety The contrast agents were evaluated for quality of diagnostic films as follows: films showing a dense concentration of contrast medium with filling and visualization of all major and minor calyces, infundibula, pelves and almost all of each ureter were listed as "good"; films showing less concentration with incomplete visualization of all portions of urinary tract but sufficient to produce diagnostically adequate films were listed as "fair"; films showing unsatisfactory visualization of urinary tract, or films which could not be interpreted, as "poor." The media were also evaluated as to incidence of the following side effects: nausea, vomiting, fainting, shock or severe reaction, hiccups, hives, pain in arm, sneezing, hot flushes, stuffiness of nose or ears.[1]



The following chart* shows comparative results of the 3 media according to age category:

quality of pyelograms and side effects expected in standard population of 1,000 patients by age, according to type of medium used

medium used and type of patient	standard population	quality of pyelograms good	fair	poor	with side effects
meglumine diatrizoate					
all ages,	1,000	827	123	50	41
0-19†	126	122	3	1	3
20-49	415	374	35	6	27
50-69	315	240	51	24	9
70 or older	144	91	34	19	2
diatrizoate sodium					
all ages,	1,000	782	134	84	72
0-19	126	115	6	5	7
20-49	415	378	26	11	40
50-69	315	227	64	24	19
70 or older	144	62	38	44	6
sodium iothalamate					
all ages,	1,000	883	81	36	54
0-19	126	122	4	0	7
20-49	415	393	20	2	29
50-69	315	269	32	14	13
70 or older	144	99	25	20	5

*Adapted from Macht[1] †In some patients in this age group, higher than recommended doses were used.

In theory: "The choice of contrast agent should ideally be individualized according to the age, sex, and disease group of the patient in order to obtain a high probability of complete visualization of the urinary tract with low probability of adverse side effects."[1]

In practice: "The choice is to be made...on the basis of the agent which gives the best concentration and the fewest side effects in the greatest number of patients regardless of age, sex, or disease category."[1]

In order of preference: Although Renografin-60 was not rated highest in all categories, the authors feel that their preference of the contrast media for intravenous pyelography would be: first, Renografin-60; second, sodium iothalamate; third, diatrizoate sodium.[1]

For brief summary of prescribing information, please refer to the end of this advertisement.

definition of safety...

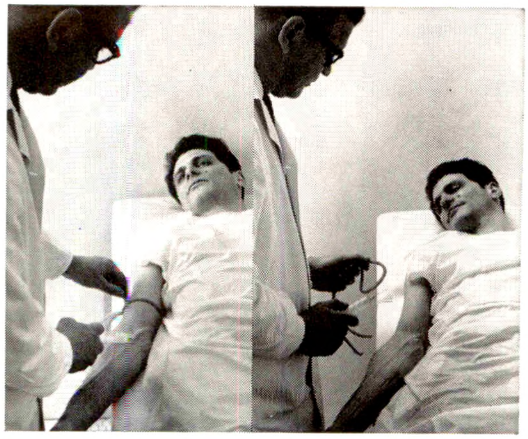
demonstrated in animals... Since meglumine diatrizoate is also used for cerebral angiography, toxicity studies of administration via the carotid artery are therefore of interest. Fischer and Eckstein[2] designed angiographic studies in animals in which procedures were very similar to clinical angiography, and which yielded data that was quantitative, graphic and nonsubjective.[2] According to the authors: "We selected the alterations in arterial blood pressure, venous pressure, heart rate and rhythm, the electrocardiogram and end-expiratory CO_2 concentration resulting from experimental cerebral angiography as refined, sensitive indications of the toxicity of a particular contrast material."[2] Their results of measured cardiovascular functions in dogs indicated that meglumine diatrizoate was far less toxic than four other contrast media.[2] As Fischer and Cornell reported in a later study: "Despite the testing of more highly concentrated solutions and larger doses, the cardiovascular responses [in dogs] from methylglucamine [meglumine] salts were much less than from sodium salts, an observation consistent with previous experiments."[3]

Other investigators have documented the comparative safety of meglumine salts in experimental studies. In order to determine reaction and tolerance of the intestines, Cooley[4] injected meglumine diatrizoate into mesenteric arteries of dogs and found no damage. Gensini *et al.*[5] reported that cardiovascular responses with it were almost identical to blood transfusions.

theory of lower toxicity with meglumine... Gensini and DiGiorgi have offered a hypothesis to explain their findings of lesser toxicity with experimental intravascular injections of methylglucamine (meglumine) salts. "When a relatively undiluted amount of sodium salts of a contrast agent is injected in an artery and carried by the blood stream toward the capillary bed, its molecules rapidly dissociate and readily diffuse through the capillary membrane and into the tissue. There, both the toxic effect of the iodine-containing organic radical and the increased concentration of sodium will readily manifest themselves. At equal concentrations of sodium, the end results will closely reflect the intrinsic toxicity of the iodine-containing organic radical on the tissues...."[5]

"In the case of the methylglucamine compounds, the same dissociation takes place. However the larger methylglucamine molecule, rich in hydrogen bonds, apparently either limits the migration of the organic radicals outside the vessel or at least minimizes their effects on the cellular metabolism."[5]

proved in practice... Paralleling similar findings in animals, clinicians have reported a generally lower



incidence of untoward reactions with Renografin-60 in urologic and cerebrovascular use. However, as with all intravascularly injected contrast agents, the possibility of severe reactions should be kept in mind (see Contraindications, Precautions and Side Effects below). In one study of over 600 urologic patients, the investigators reported that Renografin-60 produced urograms of diagnostic quality with a 6% incidence of side effects. The authors concluded: "It is hard to believe that any drug introduced intravenously could be so well borne by so many patients...."[6]

In a 74-patient study,[7] comparing Renografin-60 with diatrizoate sodium in carotid arteriography, Shealy commented: "With confused patients who are to have arteriography under local anesthesia, it is particularly desirable to have an agent that causes little pain." In this study, since "...60 per cent Renografin has resulted in considerably less pain than 50 per cent or 45 per cent [diatrizoate sodium]...we have converted to the routine use of 60 per cent Renografin for carotid arteriography; an additional 1,500 arteriograms done with 60 per cent Renografin have been quite satisfactory."[7]

better tolerated even in pediatrics... Citing some difficulties in administering contrast agents intravenously to children, Strasser *et al.*[8] selected Renografin-60 for intramuscular use in excretion urography in 16 pediatric patients because of the mild and relatively few reactions consistently associated with its use. The authors concluded: "The almost complete absence of any kind of local effect from its injection into the gluteal muscle and the absence of any serious reactions, local or systemic, indicate the safety of the medium."[8]

For brief summary of prescribing information please refer to the end of this advertisement.

definition of efficacy...

a thoroughly investigated meglumine salt Extensively evaluated for over a decade, Renografin has been consistently shown to yield a high percentage of diagnostic quality films in many phases of contrast visualization.

Upon intravenous injection, Renografin is rapidly carried to the kidneys and is so well concentrated that renal passages—including renal pelvis, ureters and bladder—may be clearly visualized. This medium also provides high contrast vasography in visualization of the cerebral vessels and the peripheral arteries and veins.

proved diagnostic excellence... In a comparative study[9] of 3 contrast agents used in cerebral angiography by Doehner (comprising a cross section of an average neurosurgical practice), Renografin-60 was equal in the arterial phase and slightly superior in the venous phase of the examination.

Findings of a previously cited study by Orr *et al.*,[6] in intravenous pyelography, also attest to the diagnostic excellence of Renografin-60. "Satisfactory roentgenograms of the kidneys were obtained in 636 (97%) of the cases, demonstrating the great diagnostic value of this procedure." And, as noted previously, Shealy found the contrast agent to be "quite satisfactory" in 1,500 carotid arteriograms.[7]

References: 1. Macht, S. H.; Williams, R. H., and Lawrence, P. S.: Amer. J. Roentgen. *98*:79 (Sept.) 1966. **2.** Fischer, H. W., and Eckstein, J. W.: Amer. J. Roentgen. *86*:166 (July) 1961. **3.** Fischer, H. W., and Cornell, S. H.: Radiology *85*:1013 (Dec.) 1965. **4.** Cooley, R. N., *et al.*: Angiology *15*:107 (Mar.) 1964. **5.** Gensini, G. G., and DiGiorgi, S.: Radiology *82*:24 (Jan.) 1964. **6.** Orr, L. M.; Campbell, J. L., and Thomley, M. W.: J.A.M.A. *169*:1156 (Mar.) 1959. **7.** Shealy, C. N.: J. Neurosurg. *20*:137 (Feb.) 1963. **8.** Strasser, N. F., *et al.*: Radiology *79*:408 (Sept.) 1962. **9.** Doehner, G. A., and Brugger, G. E.: New York J. Med. *60*:4022 (Dec.) 1960.

Contraindication

A history of sensitivity to iodine per se or to other contrast media is not an absolute contraindication to the use of meglumine diatrizoate.

Precautions and Side Effects

Severe, life-threatening reactions are rare; when they occur they suggest hypersensitivity. A personal or family history of asthma or allergy warrants special attention and may predict, more accurately than pretesting, the likelihood of a reaction, although not the type nor severity of the reaction in the individual.

The value of any pretest is questionable. The pretest most performed is the slow injection of 0.5-1.0 cc. of the preparation into a peripheral vein. An impending reaction is often indicated by transient burning and flushing, pain, "jump-like" reactions, respiratory difficulty, faintness, sneezing, itching, nausea, vomiting or urticaria. Should the test dose produce an untoward response, the necessity for continuing the examination should be re-evaluated. Antiallergic drugs may be used to advantage. In a few cases, the reactions to the test dose have been extremely severe.

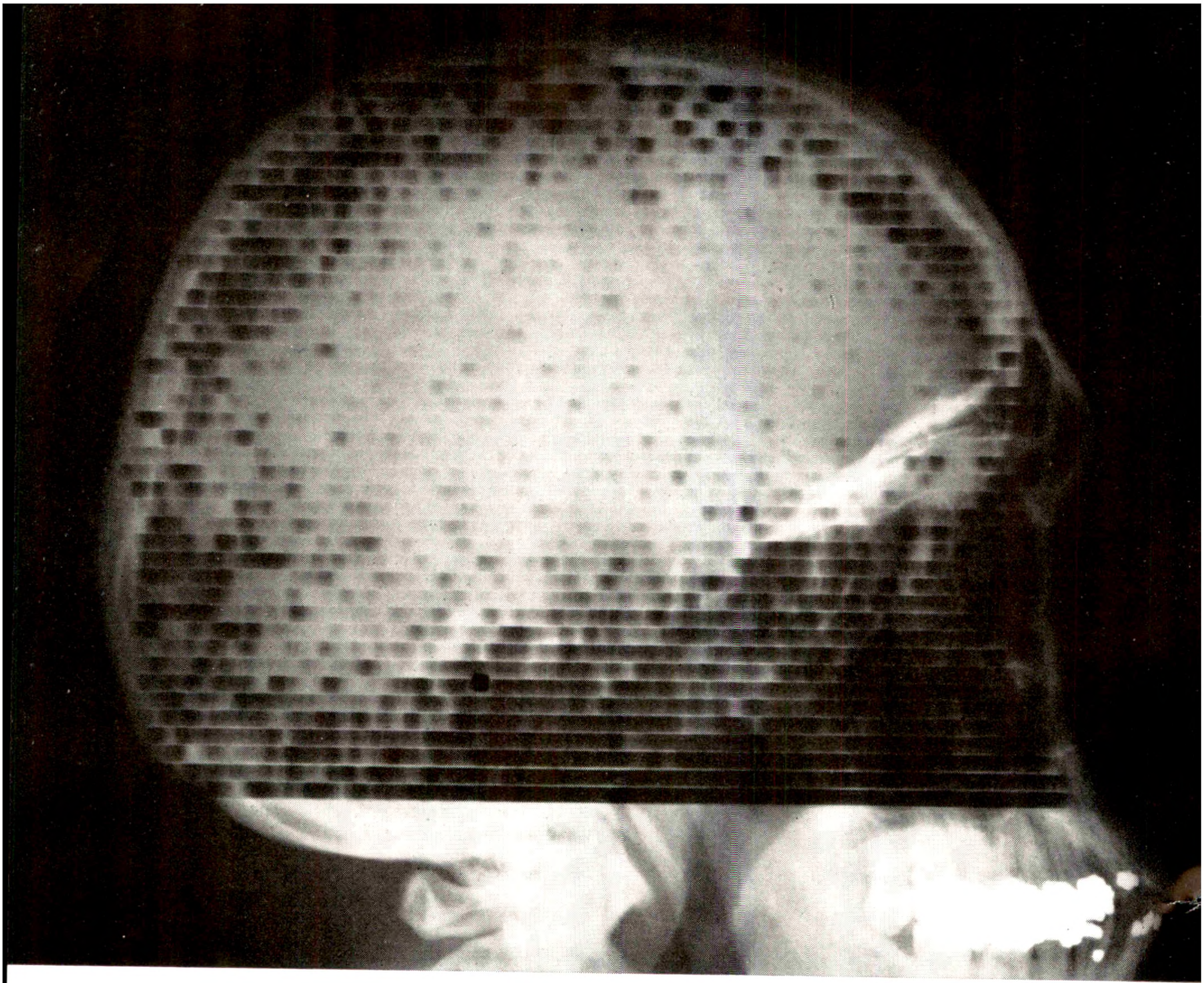
The more serious anaphylactoid reaction requires immediate treatment and may occur despite a negative sensitivity test. An emergency tray consisting of vasopressor drugs, epinephrine hydrochloride 1:1000, methoxamine (Vasoxyl) or metaraminol bitartrate (Aramine), and glucose and saline is recommended. Oxygen and instruments to guarantee a clear airway must be readily available.

Caution must be exercised, especially in cerebral angiography in extreme age, in severely debilitated patients and in those with marked or severe hypertension, advanced arteriosclerosis, cardiac decompensation, recent cerebral embolism, or thrombosis, chronic pulmonary emphysema and in cyanotic infants.

For full details the Package Insert should be read.

Supply: Renografin-60 is supplied in vials and ampuls as a sterile aqueous solution providing 60% meglumine diatrizoate containing approximately 29% firmly bound iodine.

Available in 30 cc. vials or 25 cc. ampuls.



Abbott announces Pertscan™-99m

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SPEED: Gives each projection fast—15 minutes or less with rectilinear scanners, 2 to 4 minutes with a camera.

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SAFETY: Carrier-free, non-pyrogenic, sterile, and isotonic.

FLEXIBILITY: Oral or intravenous administration in two sizes: 10 millicuries in 4 ml. and 15 millicuries in 6 ml.

SHIPMENTS: Monday through Friday—and Sunday . . . allows scheduling of brain scans 6 days a week—Monday through Saturday.

INDICATIONS: Adjunctive diagnostic aid in detecting and localizing intracranial neoplastic (primary or metastatic) and non-neoplastic lesions.

CONTRAINDICATION: Radio-pharmaceutical agents should not be administered to pregnant women or to persons less than 18 years old unless the indications are very exceptional.

PRECAUTIONS: Care should be taken to ensure minimum radiation exposure to the patient as well as all personnel; to prevent extracranial contamination because this can lead to erroneous interpretation; and to differentiate areas of abnormal activity from areas of normal vascular activity.

801391

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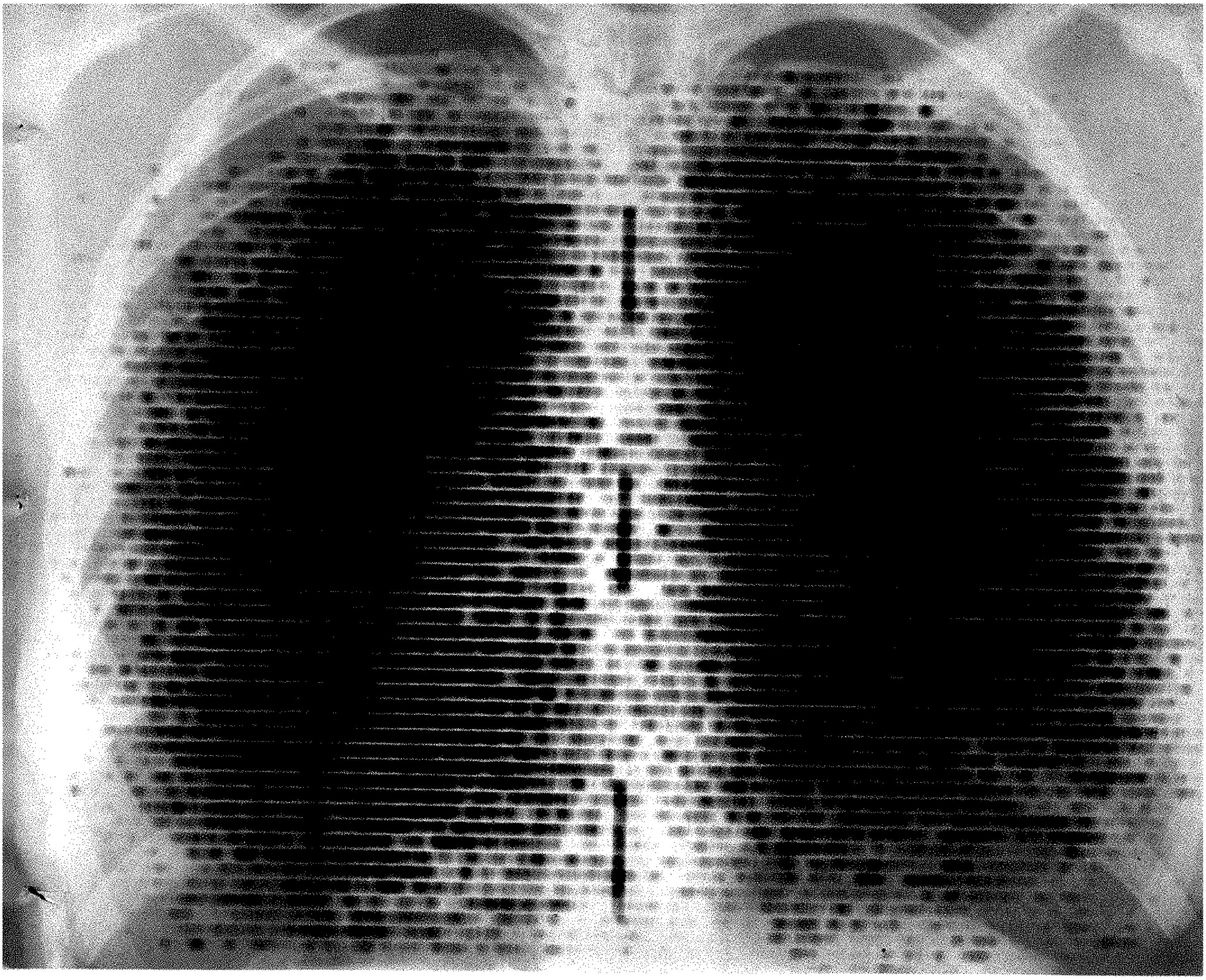

Abbott announces Macroscan™-131

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Pulmonary embolism, suspected: To confirm (or rule out) its occurrence.

Chronic pulmonary tuberculosis: To estimate unilateral and regional function and perfusion of the lungs.

Emphysema: To evaluate the degree of focal lack of perfusion.

Pneumonitis: To evaluate the decreased regional blood flow that occurs without obstruction of vessels.

Lung tumors: To evaluate the regional ischemia resulting from compression or obstruction of pulmonary arteries.

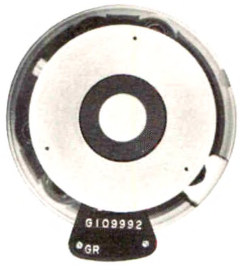
Surgery and/or other therapy for lung disorders: To evaluate the effectiveness of therapeutic measures.

Macroscan-131 is sterile and non-pyrogenic. It is ready to use and should not be heated prior to use.

INDICATIONS: For scintillation scanning of the lungs to evaluate total, unilateral, and regional arterial perfusion to the lungs.

CONTRAINDICATION: Radio-pharmaceutical agents should not be administered to pregnant women, nursing mothers, or to persons less than 18 years old unless the indications are very exceptional.

PRECAUTIONS, SIDE EFFECTS: Care should be taken to administer the minimum dose consistent with safety and validity of data. The possibility of an immunological response to albumin should be kept in mind when serial scans are performed. There is a theoretical hazard in acute cor pulmonale, because of the temporary small additional mechanical impediment to pulmonary blood flow. A possible case of urticara has been related to a similar preparation. The thyroid gland should be protected by prophylactic administration of concentrated iodide solution.



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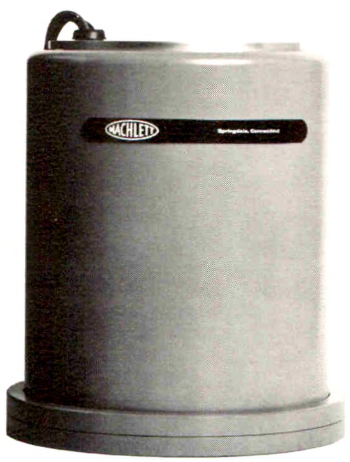

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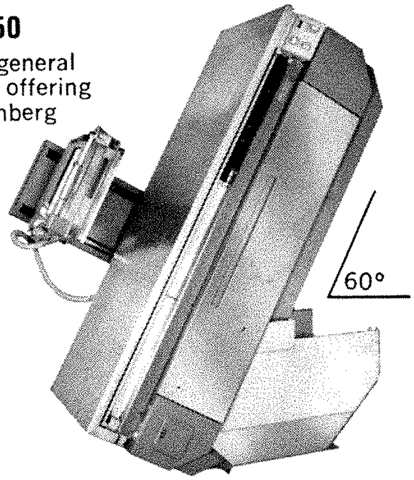

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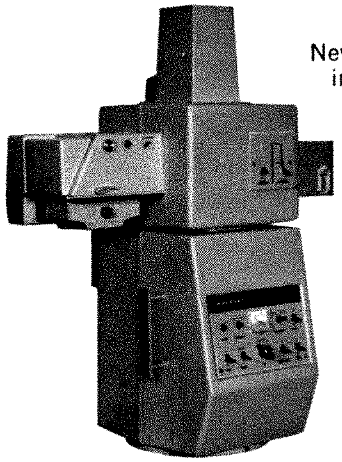

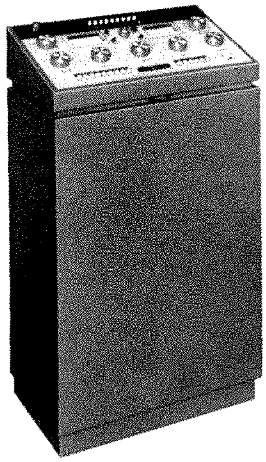

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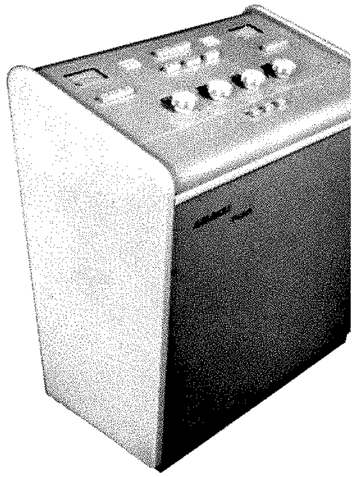

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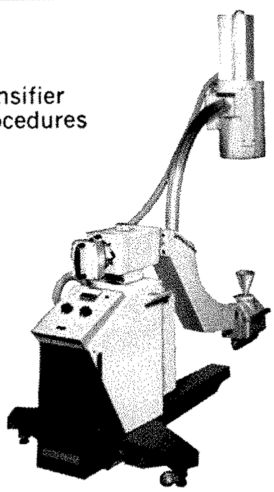

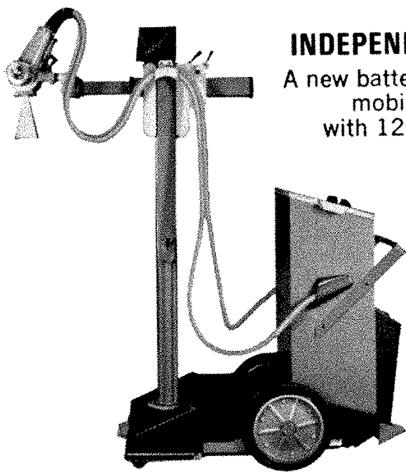

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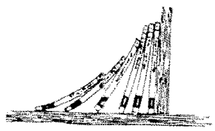

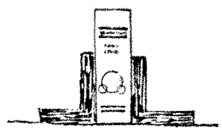

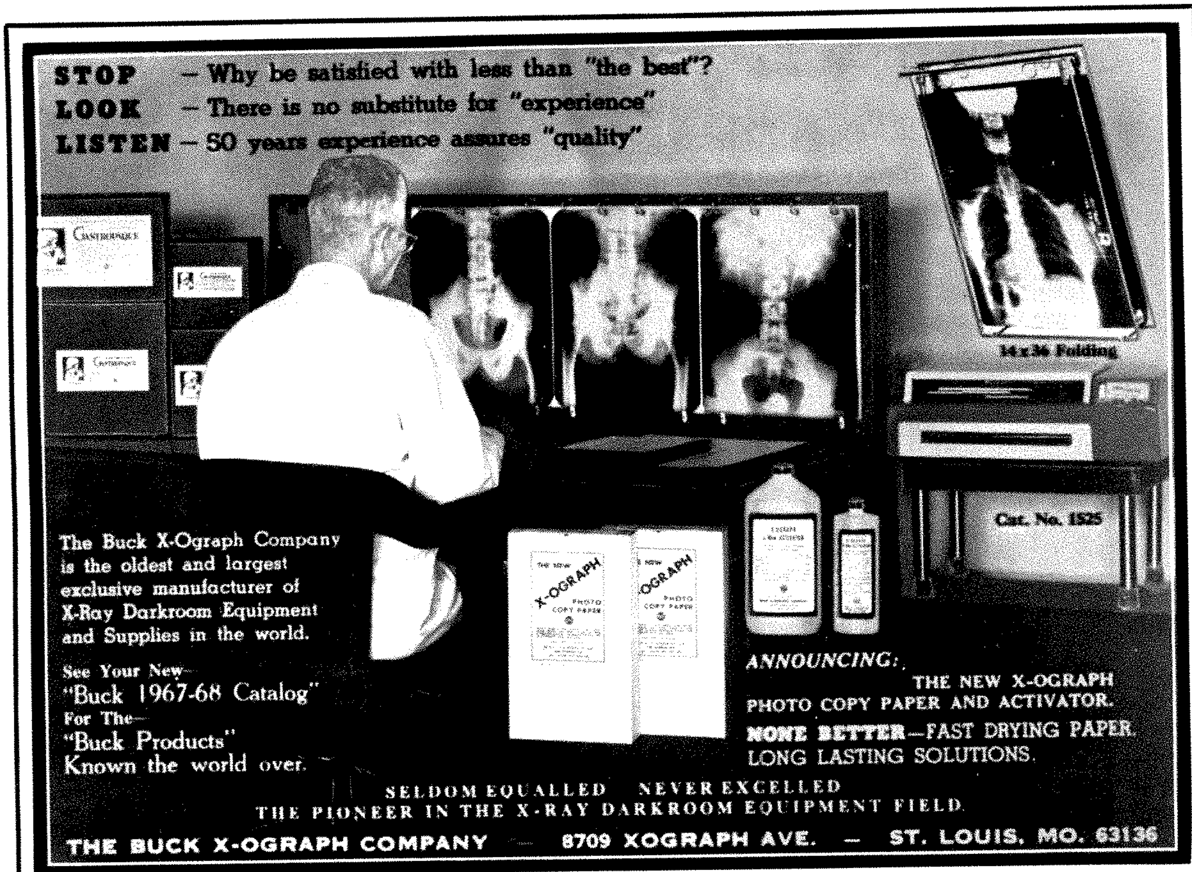

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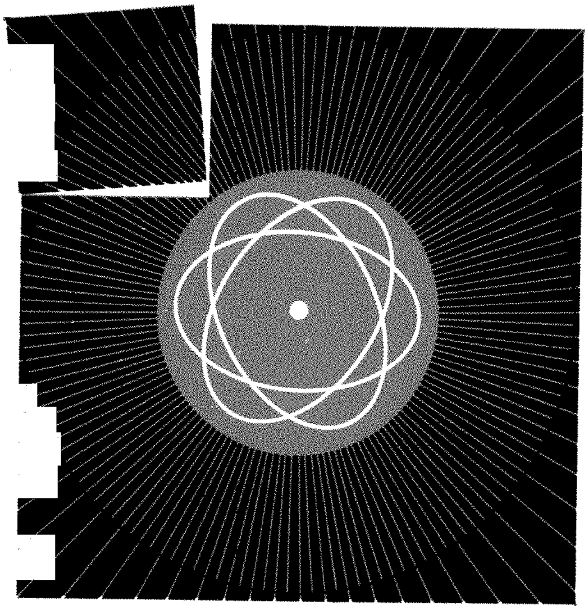

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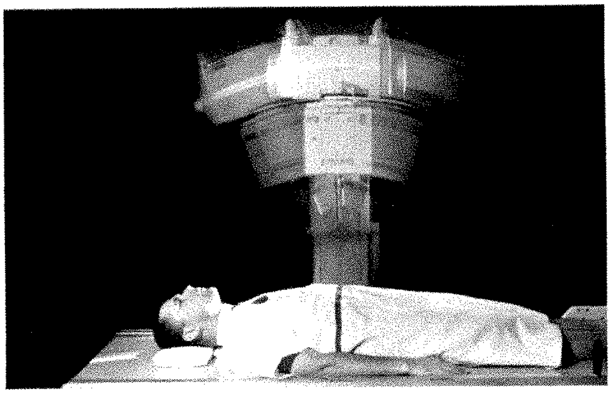

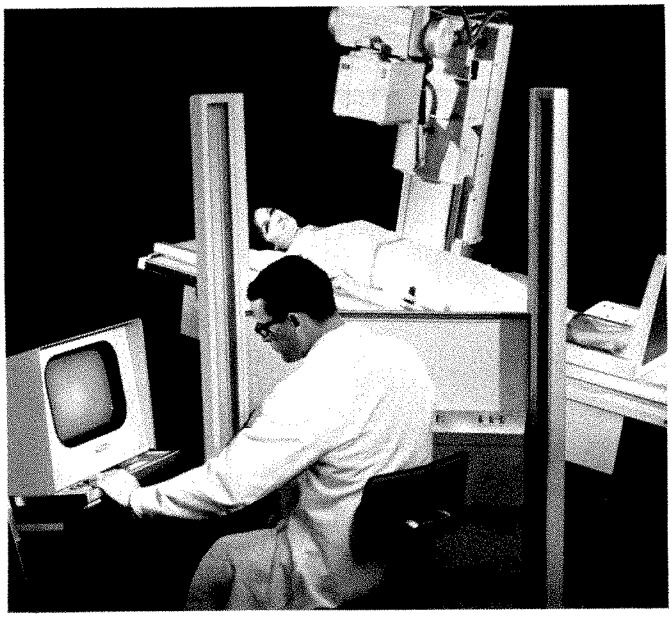

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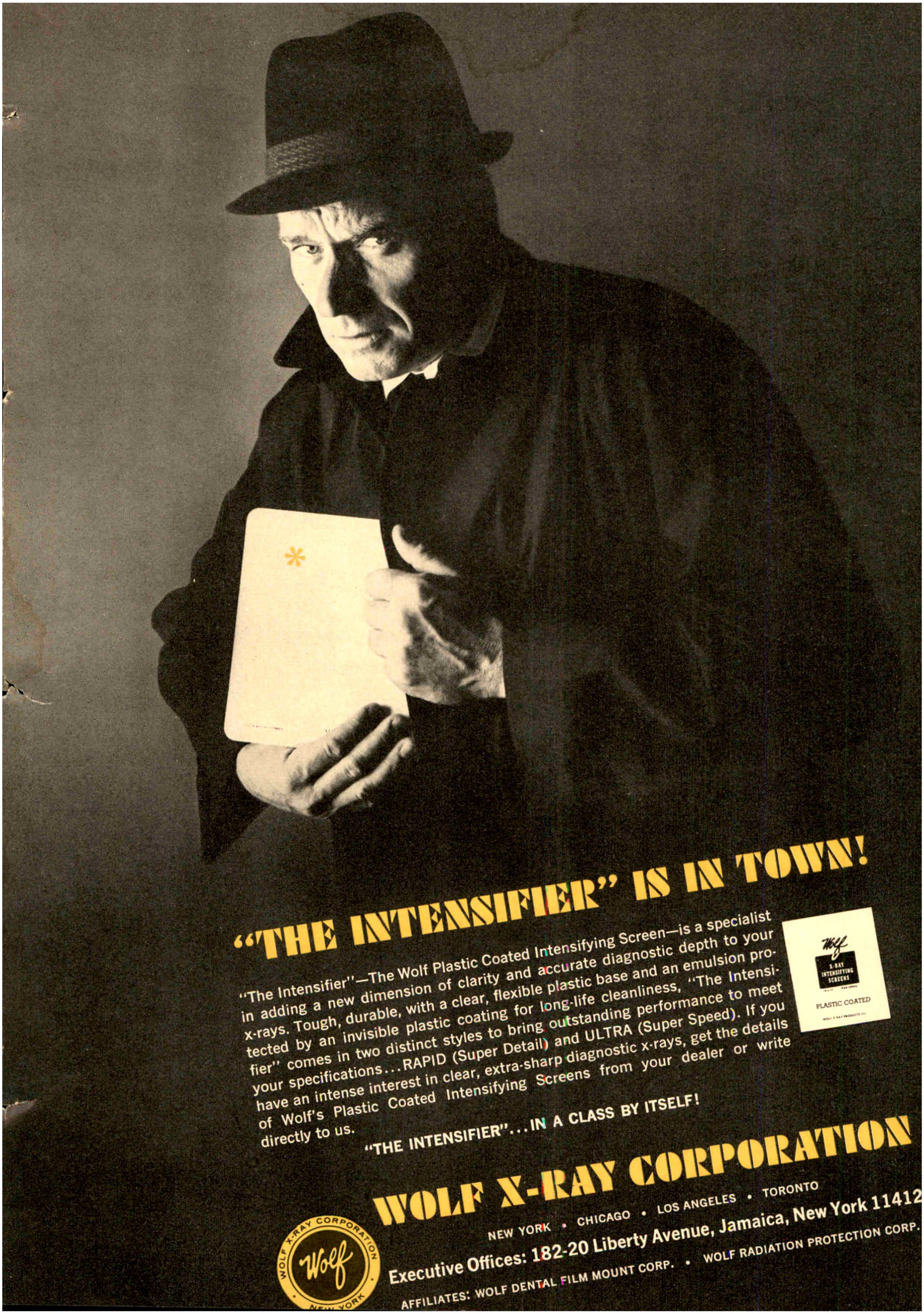
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VOLUME 102 FEBRUARY, 1968 NUMBER 2

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April 7-11, 1968
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6. Safely – *Patient* safety derives from points 2 and 3 above and this: *every* elution is easily and precisely checked for possible molybdenum breakthrough; simple, accurate radioassay materials are included for testing all elutions. *Hospital personnel* safety is related to point 5 above since speed reduces exposure, and: the generator never leaves its ¾″ lead shield or its 6 inch diameter can; and the construction is unbreakable.

7. Reliably – Semi-automatic operation eliminates the risk of improper elution with the wrong solvent, the wrong volume of solvent, or at the wrong rate. (See also: most other points above.)

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VOL. 102 FEBRUARY, 1968 No. 2

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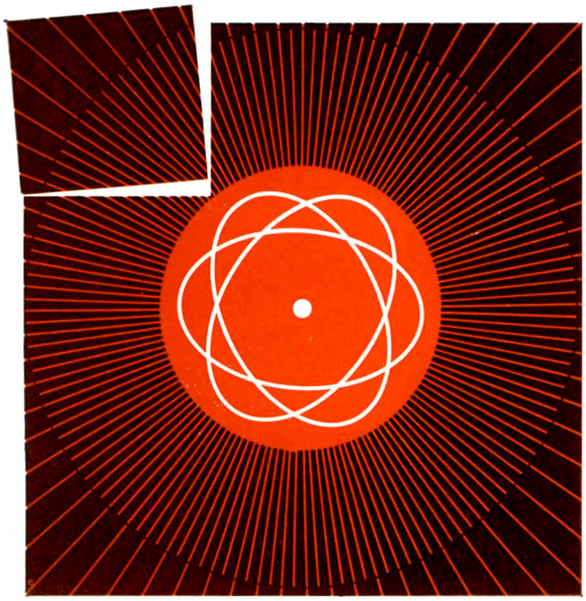
SQUIBB

a research concept in radiopharmaceuticals

Are you ordering radioisotopes piecemeal?



Are you ordering separately after each referral and then rescheduling the patient? Most drugs are on hand when the patient needs them. Why not radiopharmaceuticals?

If a hospitalized patient needs blood, he can have it within minutes. If an ill patient needs penicillin, it can be prescribed immediately. But if he should need a radio-diagnostic test, he may have to wait several days for the material to arrive.

There was a time when such waiting was necessary, but no longer. Many of the available radio-pharmaceuticals have now reached the stage when they can be integrated into the mainstream of medical and hospital practice and can be "at hand" when needed. In particular, the unique 5-day precalibration of Squibb radioisotopes makes the need for ordering separately after each referral a thing of the past. Most laboratories can pretty well estimate what their approximate weekly need will be, so that everything can be ordered in one shipment to arrive on any given day. Thus, when a patient is referred, the diagnostic agent is already on hand and the test can be run immediately. Moreover, there is only one shipping charge. And if the material arrives for use during the latter part of the working week, Squibb will bear the cost of radioactive decay over weekends.

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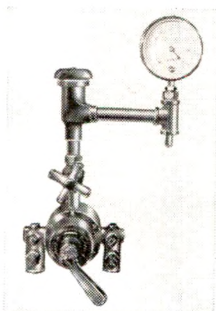

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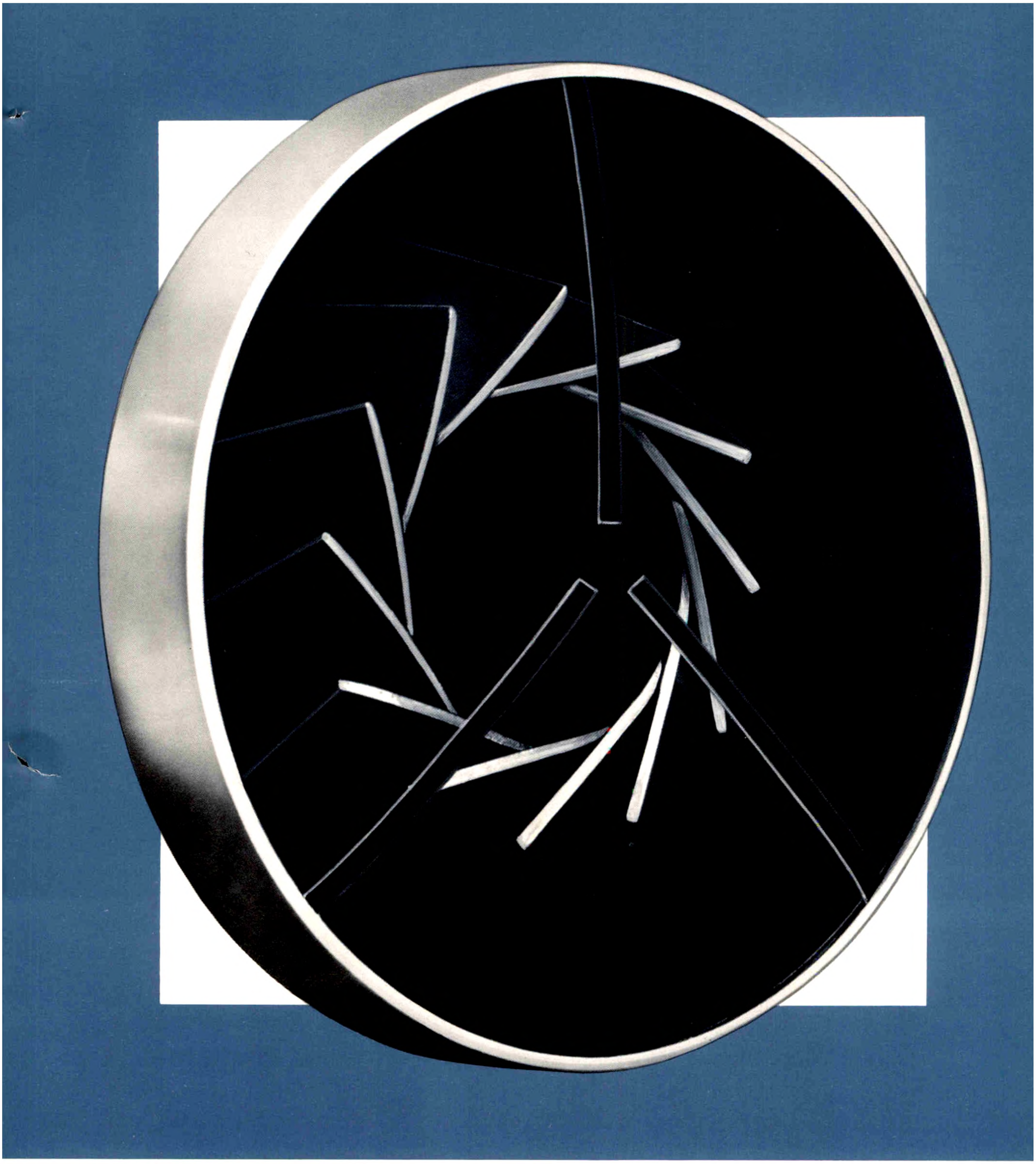

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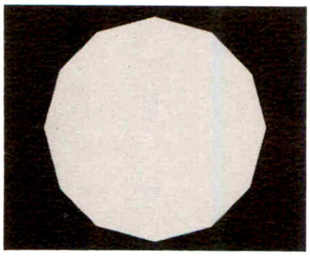
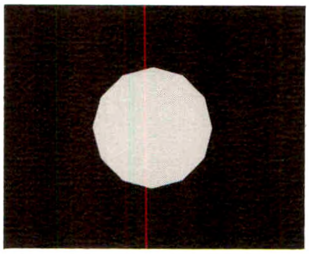
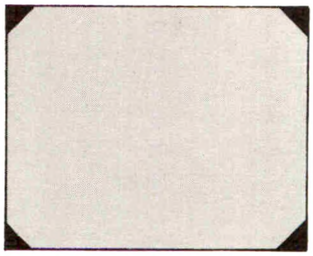


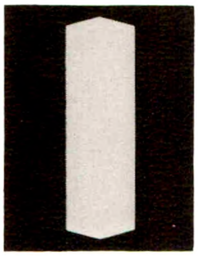
Routine
image areas
(gall bladder)



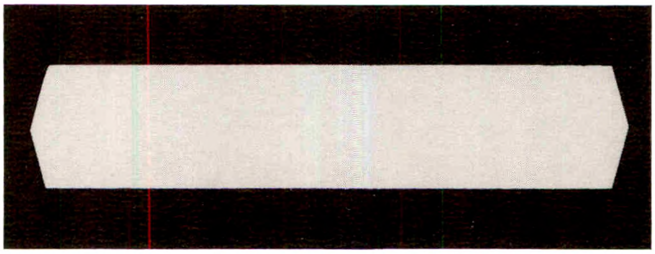
High definition
image areas
(sinus & mastoids)



Typical large
area coverage
(abdomen)



Selective
area coverage
(esophagus)



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technique coverage
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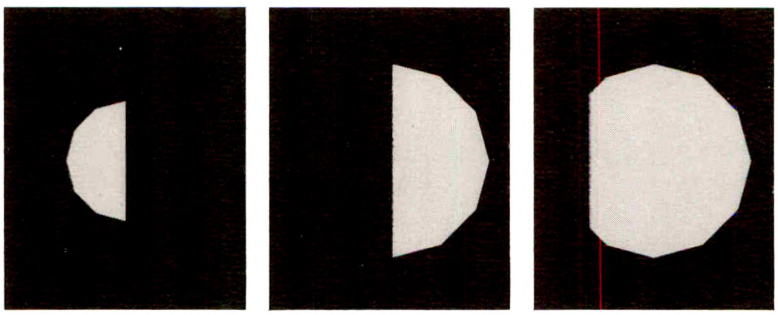
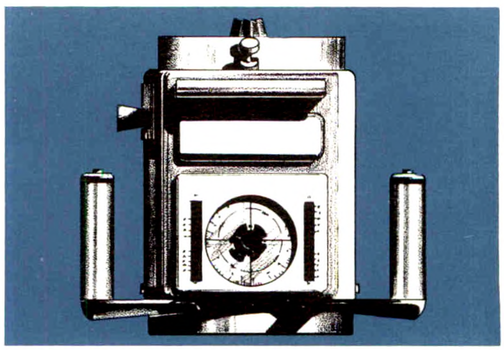


Special beam shapes
(mammography)



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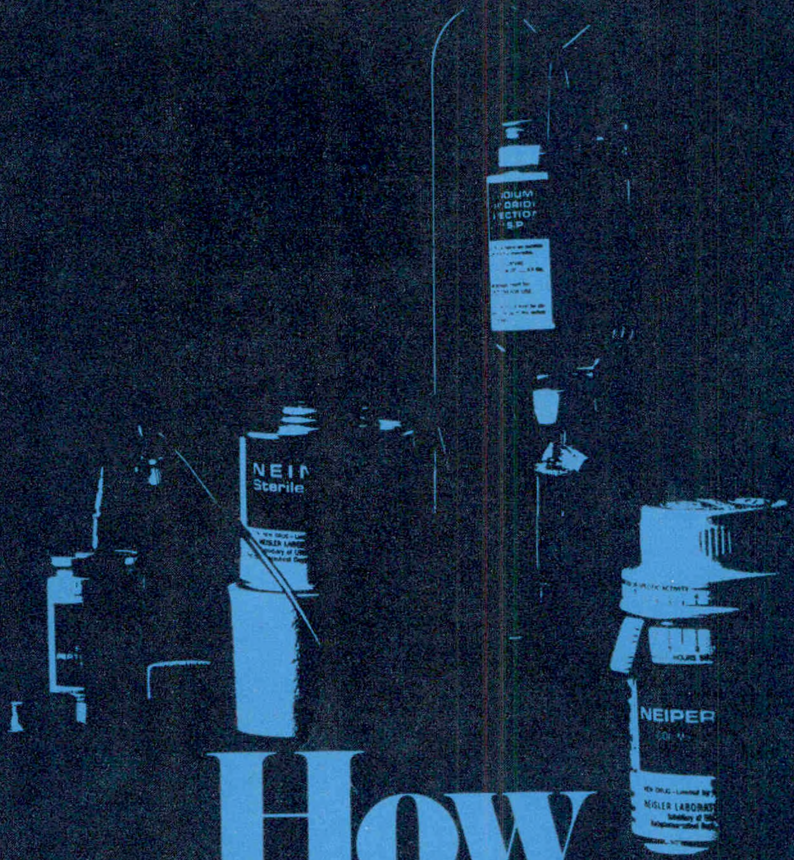

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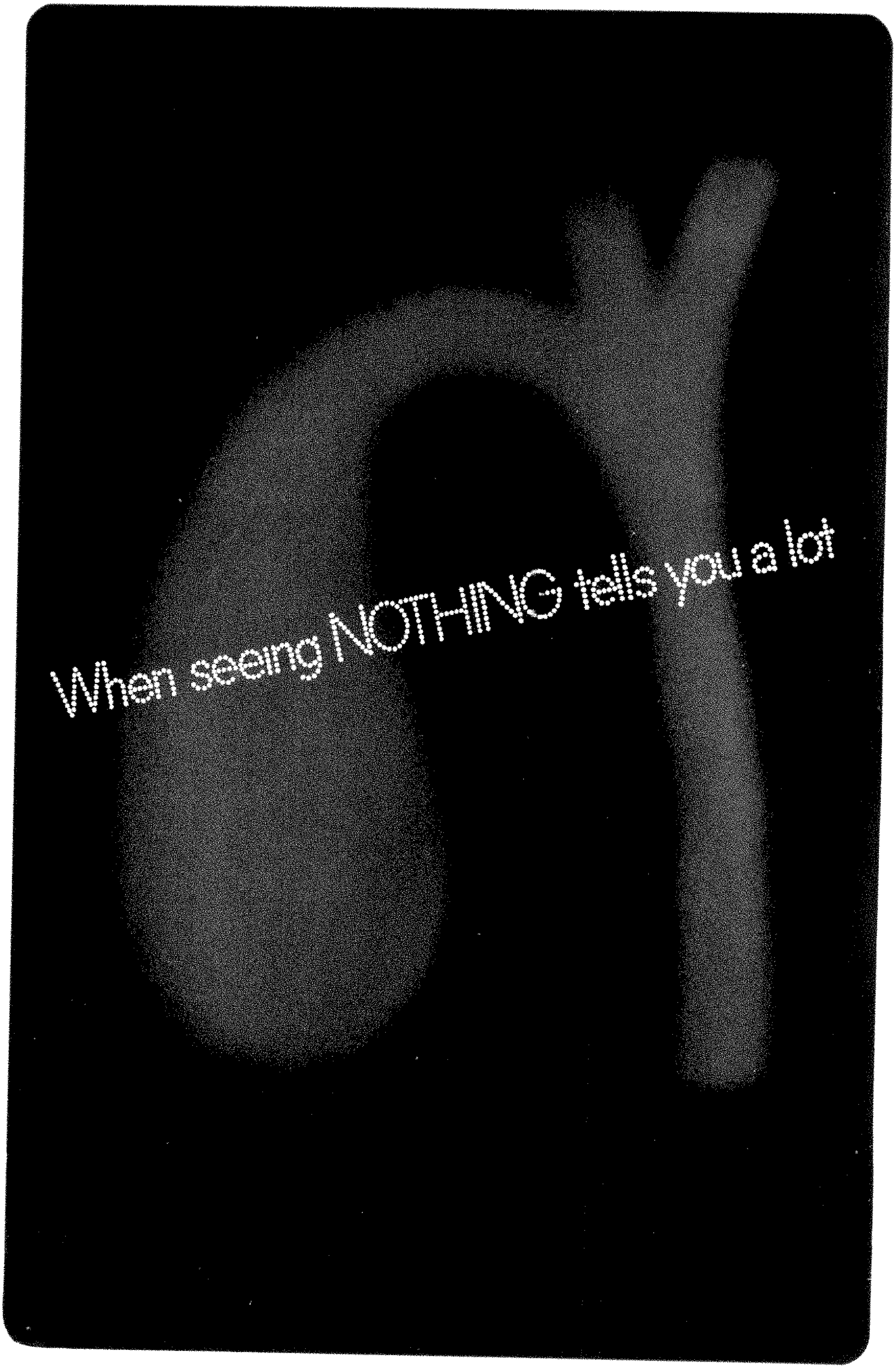
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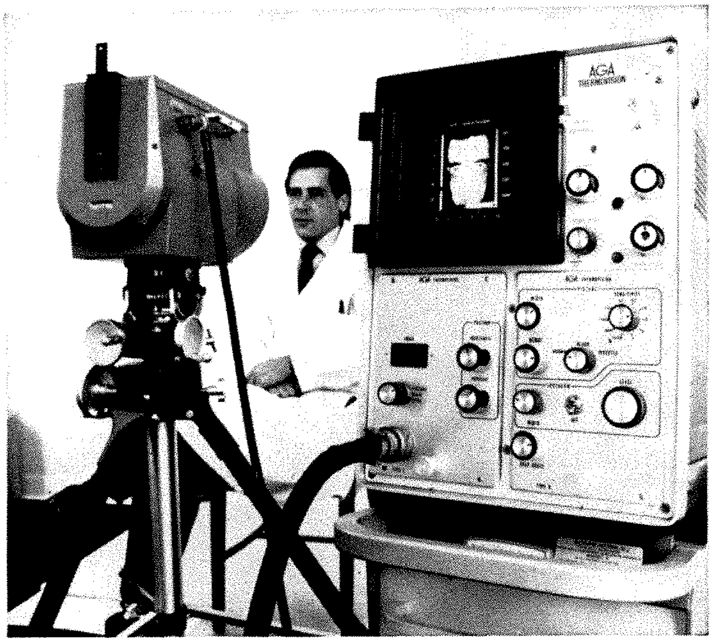

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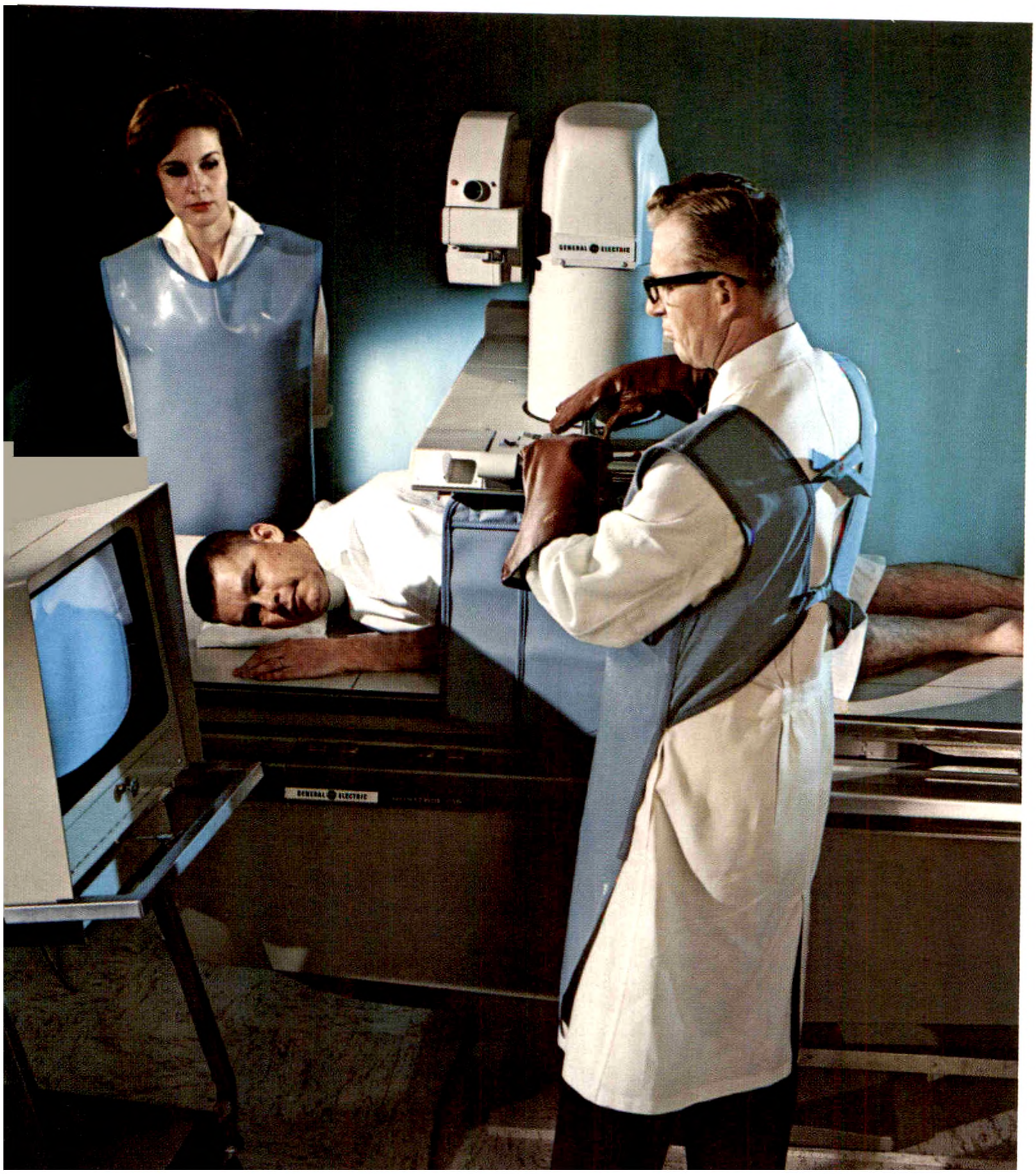

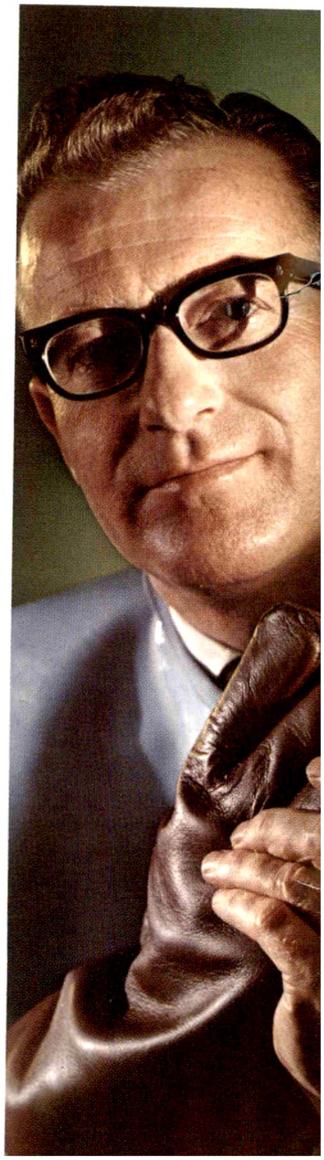

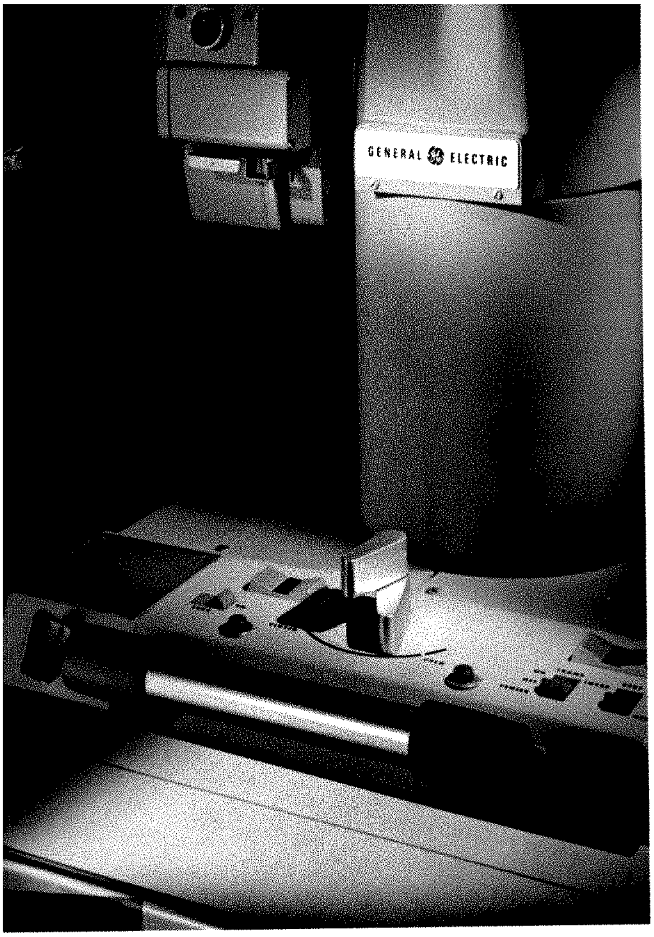

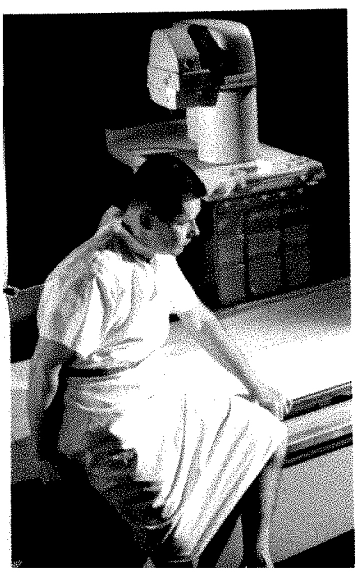

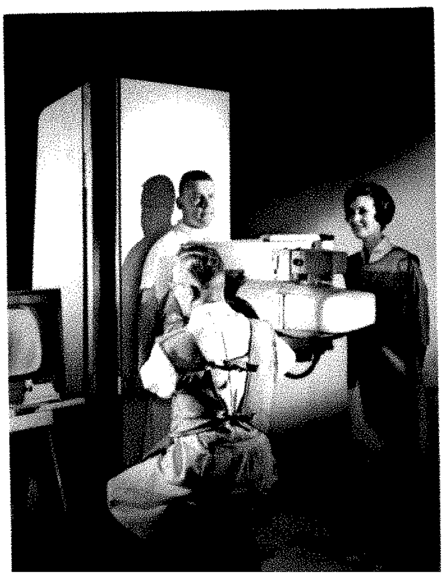

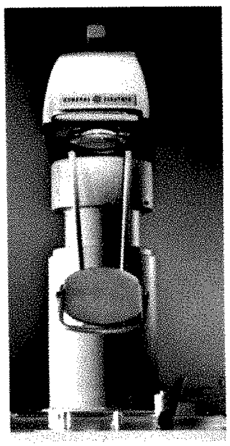

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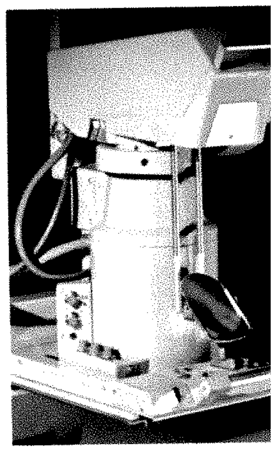
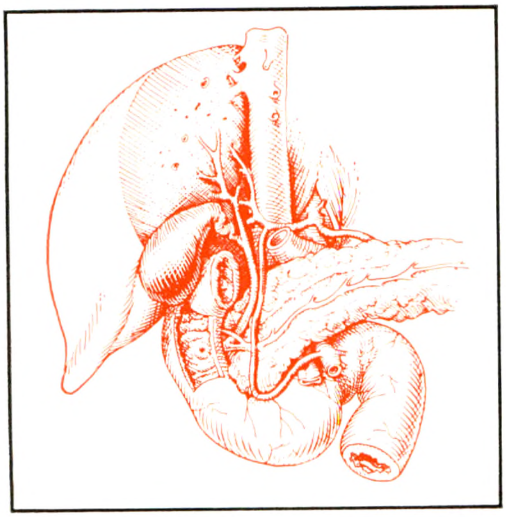
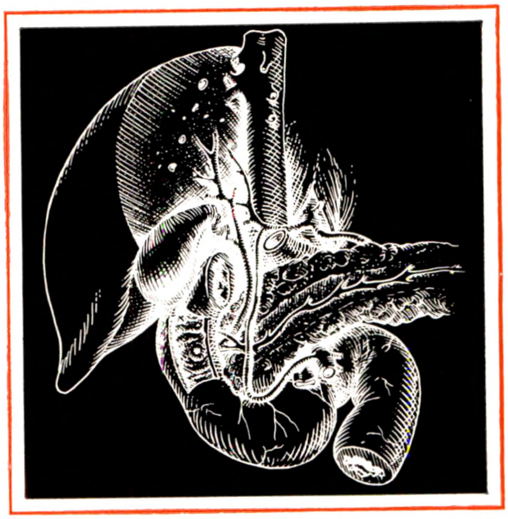


FLUORICON II

a research concept in contrast visualization

for better definition of disease: documenting differences between oral contrast agents





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maximum concentration with better patient toleration in oral cholangiography and cholecystography

For rapid or routine studies of the gallbladder and biliary ducts, Oragrafin provides rapid, more complete absorption, for maximum concentration and excellent contrast.

definition of maximum concentration

high absorption index—"No one will dispute the statement that the diagnostic reliability of oral cholecystography depends upon the degree of absorption of the contrast medium employed."[1] Radioisotope studies with ipodate sodium show a markedly improved absorption index (approximately 70 per cent) with no increase in the toxic properties.[1]

less bowel residue—"Incomplete and variable absorption of a cholecystographic agent is not desirable, for the opacification of the gallbladder is then less dependent on the status of the gallbladder and more a reflection of the percentage absorption."[2] "Opaque material in the bowel was found in 46 per cent of [105 patients in] the... [iopanoic acid] group as compared with 9 per cent of those [99] of the [Oragrafin Sodium Capsules]...group."[2] In another study, 49 of 100 patients receiving iopanoic acid had residue in the gastrointestinal tract, while only 15 of 100 patients receiving Oragrafin had such residue.[3]

excellent opacification—"In addition to its ease of administration and safety, its principal advantages are a high yield of diagnostic films...."[4]

definition of better toleration

low incidence of untoward reactions—In contrast to findings with other cholecystographic agents, Lewitan and Garcia[5] reported in their 246 patient study: "With

ipodate calcium...there was no clinical evidence of immediate or delayed nephrotoxicity in any of the patients given it...."[5] To study possible renal toxicity, "Creatinine clearance tests were also done before and after administration of multiple doses in excess of 6 gm. in 8 cases, and showed no significant alterations."[5] However, "Multiple doses beyond 6 gm. are not recommended."[5] In their study of 120 patients, Glenn and O'Brien reported "...no reactions in this series of patients attributable to the administration of [Oragrafin]...."[4] And, McCrory reported that Oragrafin was "...used routinely in cholecystographic studies in approximately 2000 patients with excellent diagnostic films and only rare and mild reactions."[6]

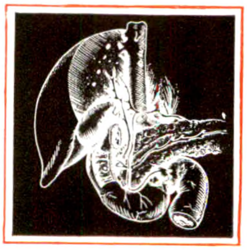
side effects compared to iopanoic acid

side effects encountered in administration of 3 Gm. of Oragrafin Sodium Capsules and 3 Gm. iopanoic acid*

	Oragrafin Sodium Capsules (Squibb Sodium Ipodate)	iopanoic acid
no. of cases	99	105
no. of side effects		
nausea		
slight	10	14
severe	2	6
vomiting	0	1
diarrhea		
mild	7	22
severe	3	16
cramps	5	15
dysuria	9	13
total/per cent	36 (36.3%)	87 (82.9%)

*Adapted from White, W. W., and Fischer, H. W.[2]

Juhl,[3] in his study of 200 patients (100 on each agent), found no significant difference between iopanoic acid and sodium ipodate in the incidence of nausea; vomiting occurred in an equal number of cases.



definition of convenience:

Oragrafin® Calcium Granules

Squibb Calcium Ipodate

visualization of poorly functioning gallbladder reduces the need for I.V. studies—In a concentrating gallbladder, Oragrafin Calcium Granules (Squibb Calcium Ipodate) will show storage, concentration, delivery or stones. A patent biliary duct can generally be expected to visualize. Provided the cystic duct is patent, Oragrafin will visualize the normal gallbladder, the abnormal gallbladder containing papillomata, nonopaque stones or radiodense calculi, and gallbladders where concentrating power is diminished.

patient convenience—Routine cholecystography night-before procedure is easy for patients to follow; palatable granules further enhance patient acceptability. Rapid clearance of medium permits same-day administration and gallbladder and ductal films, and, if necessary, same-day re-examination; reduces need for I.V. studies.

Optimal concentration in the hepatic and biliary ducts usually occurs within 1 to 3 hours. Although the gallbladder is optimally opacified 10 hours after ingestion of the agent, diagnostically valuable information can often be obtained within 5 hours or less.

rapid absorption permits same-day re-examination—To determine the cause of nonopacification after routine cholecystography, most physicians require re-examination by repeating the procedure at a later date (sometimes doubling dose), or

A 2693

by administering more agent the evening of the first unsuccessful examination (again sometimes doubling dose), and repeating the study the next day. "The advantage of the calcium ipodate method is that the examination can be completed in five additional hours with a limited dose of contrast agent."[7]

a valuable medium for peroral cholegraphy[5]—Rapidly absorbed from the gastrointestinal tract, calcium ipodate has been reported by some investigators to be diagnostically superior to other oral cholangiographic contrast agents. With careful timing of the examination and the use of tomograms or laminograms, the frequency of good results can approximate that obtained with intravenously administered agents. According to Lewitan and Garcia,[5] the medium's relative safety makes it a valuable medium for peroral cholegraphy. Timesaving and economical Oragrafin Calcium Granules may be particularly useful in certain patients for whom I.V. radiography presents potential hazards, such as elderly patients, those with cardiovascular disease, or patients who may exhibit sensitivity to the test dose of an intravenous agent.

Unique among oral media, Oragrafin Calcium Granules permits same-day films of the gallbladder and ductal system.

dosage schedule for films of gallbladder and ductal system

8 A.M.	2 packets of granules
9 A.M.	visualization of ducts
10 A.M.	optimal visualization of ducts
1 P.M.	visualization of gallbladder

References: 1. Sanen, F. J.: Amer. J. Roentgen. *88*:797 (Oct.) 1962. **2.** White, W. W., and Fischer, H. W.: Amer. J. Roentgen. *87*:745 (April) 1962. **3.** Juhl, J. H., *et al.*: Radiology *80*:87 (Jan.) 1963. **4.** Glenn, J. C., Jr., and O'Brien, P. S.: Southern Med. J. *56*:167 (Feb.) 1963. **5.** Lewitan, A., and Garcia, J. F.: Amer. J. Dig. Dis. *10*:219 (March) 1965. **6.** McCrory, E.: J. Tenn. Med. Ass. *58*:258 (Aug.) 1965. **7.** Crummy, A. B.: Wisconsin Med. J. *65*:84 (Feb.) 1966.

Contraindications: Contraindicated for persons sensitive to oral iodine compounds or for patients with combined renal and hepatic disease or severe kidney impairment. Gastrointestinal disorders, which may interfere with absorption, or liver dysfunction, which may result in inadequate biliary secretion of medium, are likely to result in unsatisfactory visualization.

Precautions and Side Effects: Mild and transient nausea, vomiting, or diarrhea sometimes occur; but the incidence can be reduced by using the calcium granules and restricting the dosage to 3 Gm. Transient headache, dysuria, or abdominal pains may occur.

Hypersensitivity reactions may include urticaria, serum sickness-like reactions (fever, rash, arthralgia), other skin reactions, and rarely anaphylactoid shock. They are more likely to occur in the individual with a history of allergy, asthma, hay fever, or urticaria and in the individual who is known to be hypersensitive to iodine compounds. Antihistamines and corticosteroids are used to control hypersensitivity reactions; but the occasional serious anaphylactoid reactions require the immediate use of epinephrine or phenylephrine, oxygen, and intravenous corticosteroids.

For full information see Package Insert.

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in oral cholangiography and cholecystography

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for maximum concentration with better patient toleration

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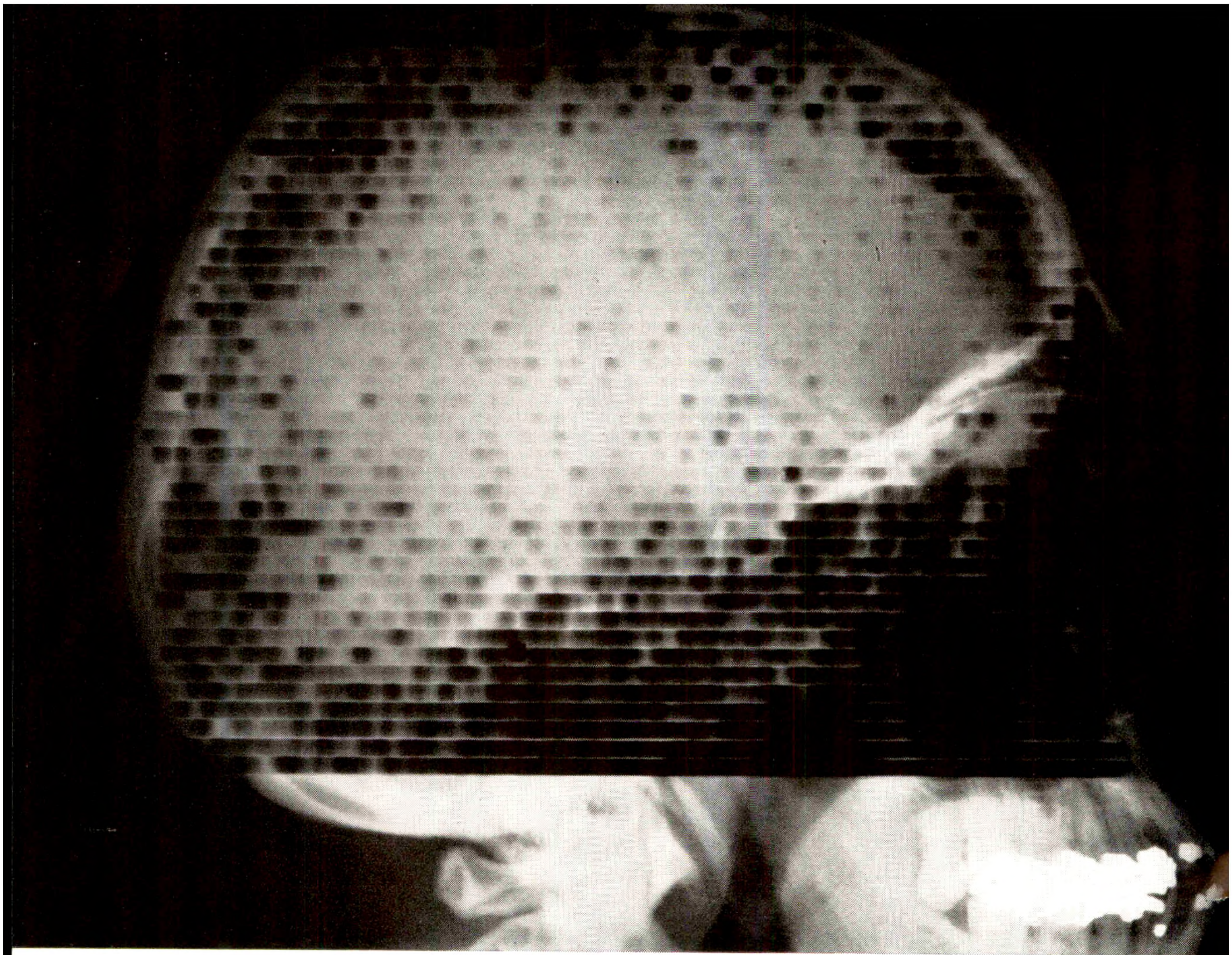

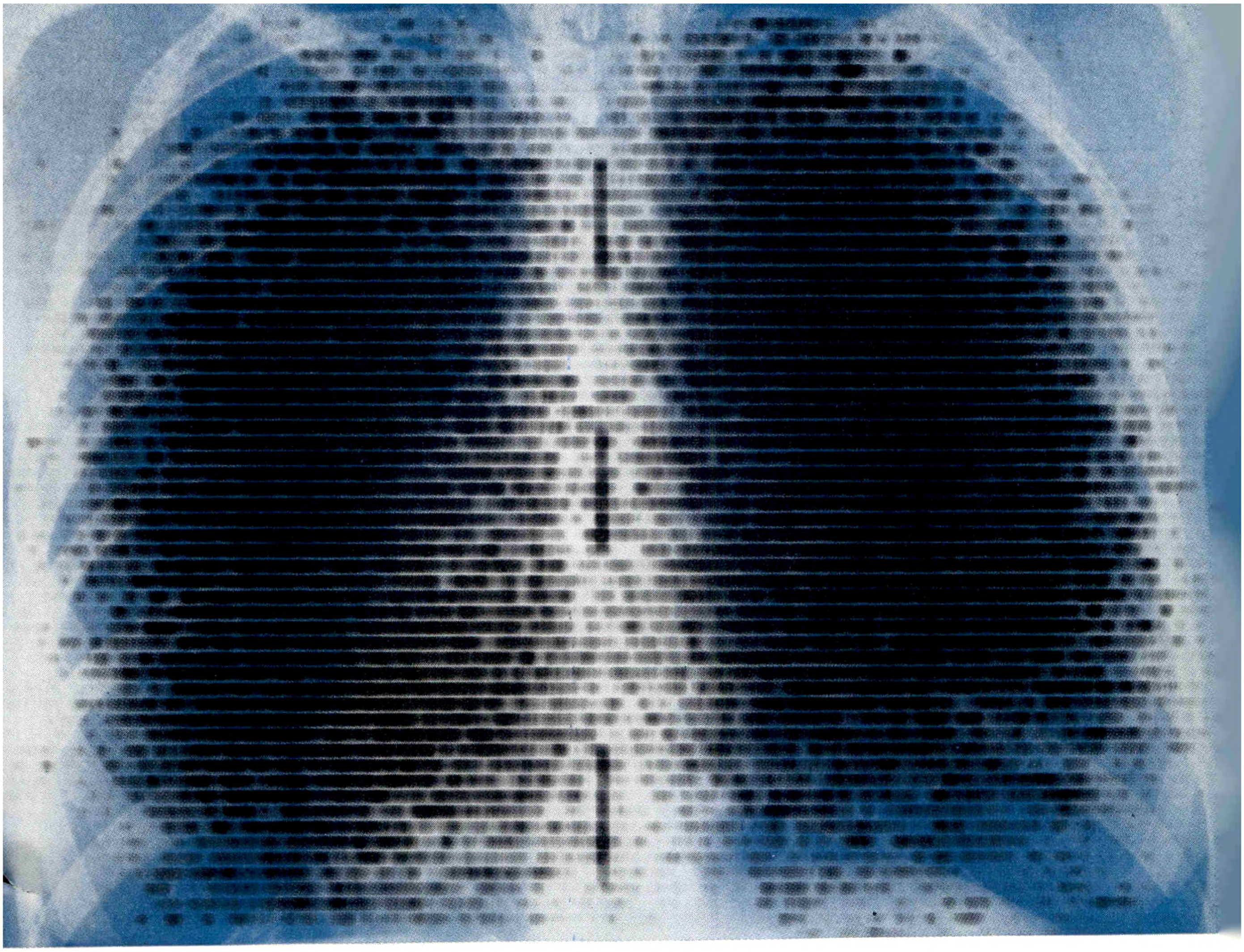

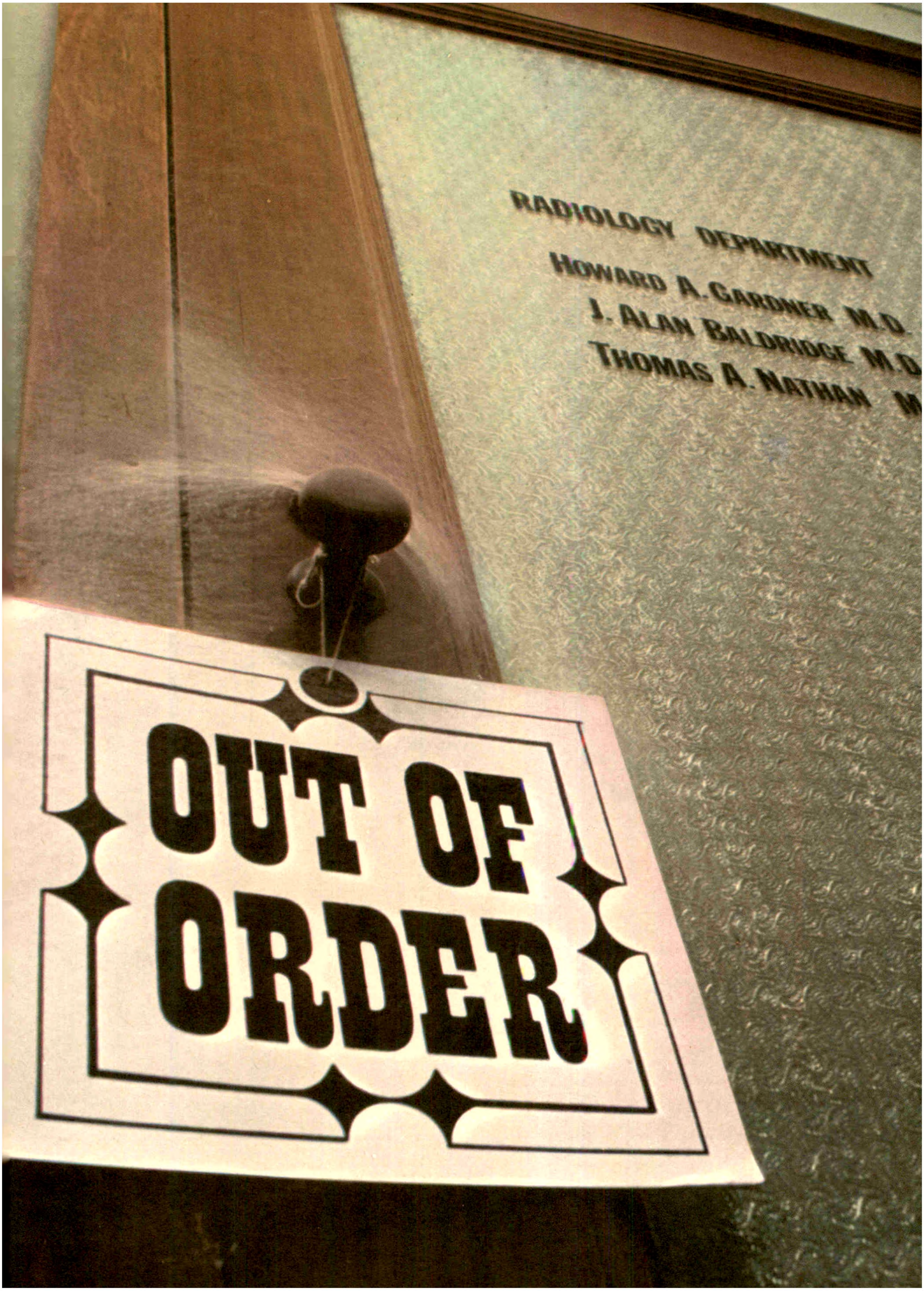
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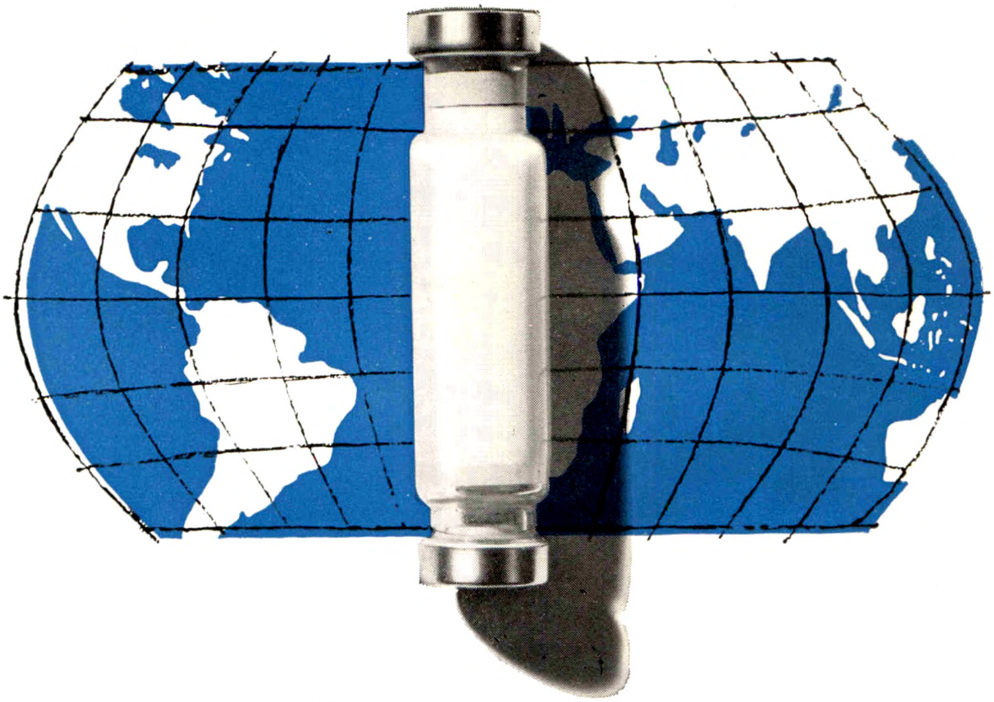

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MILLIONS OF RADIOGRAPHS AND THOUSANDS OF INSTALLATIONS LATER: A FULL REPORT ON THE KODAK RP X-OMAT® SYSTEM

These year-and-a-half figures show Kodak 90-second processing has been widely accepted by the medical community. Various studies and reports by radiologists are now in, and they begin to show the reasons for the overwhelming acceptance of the revolutionary Kodak 90-second processing system.

In brief, the consensus is that while maintaining quality, it saves wear and tear—on patients, radiologists, support personnel, and hospital facilities. It means greater efficiency, better patient care, capability to handle increased case loads in existing facilities, reduced examination-room occupancy per patient. And it means radiographs of the same uniformity, high image quality, and diagnostic reliability radiologists have been expecting and getting from Kodak for years.

All of this is easy to claim, of course. But it's borne out by studies and reports from radiologists who have used the system for more than a year. Let's look briefly at some statistics.

Increased efficiency

According to an early study, it was projected that 90-second processing could mean the capability to handle an 18-percent work-load increase over conventional 7-minute processing. In dispersed processing installations (an *RP X-Omat* Processor for each two examining rooms) it was calculated that, on the average, examination-room occupancy could be reduced up to 25 percent; in terms of additional work-load capacity, that would mean an increase in patients per day of 31 percent over 7-minute central processing. Radiologists using the Kodak 90-second processing system have found that it has more than lived up to the predictions of this study.

Patient benefits

In terms of the patient, virtually immediate delivery of dry, ready-to-read films means greater comfort, better care. There's no more shuffling patients in and out of examination rooms while waiting for film-adequacy checks; and because of immediate adequacy checks, there are no more patient call-backs. In terms of patient comfort, there's reduced time under anesthesia, no hall waiting, and less time away from the patient's bed. This increased patient comfort is particularly evident in serial examinations.

Radiologist benefits

The Kodak 90-second processing system gives the radiologist the precious gift of time. As the number and complexity of radiological examinations grow (and the shortage of radiologists becomes more acute), the demands upon a radiologist's time increase proportionately. Almost immediate availability of finished films permits greater utilization of examining rooms, thus extending the effective time of the radiologist and his staff. Time-consuming patient call-backs are eliminated, as radiographs can be checked before patients leave the examination room. Just as important, the radiologist has better control of radiographic quality.

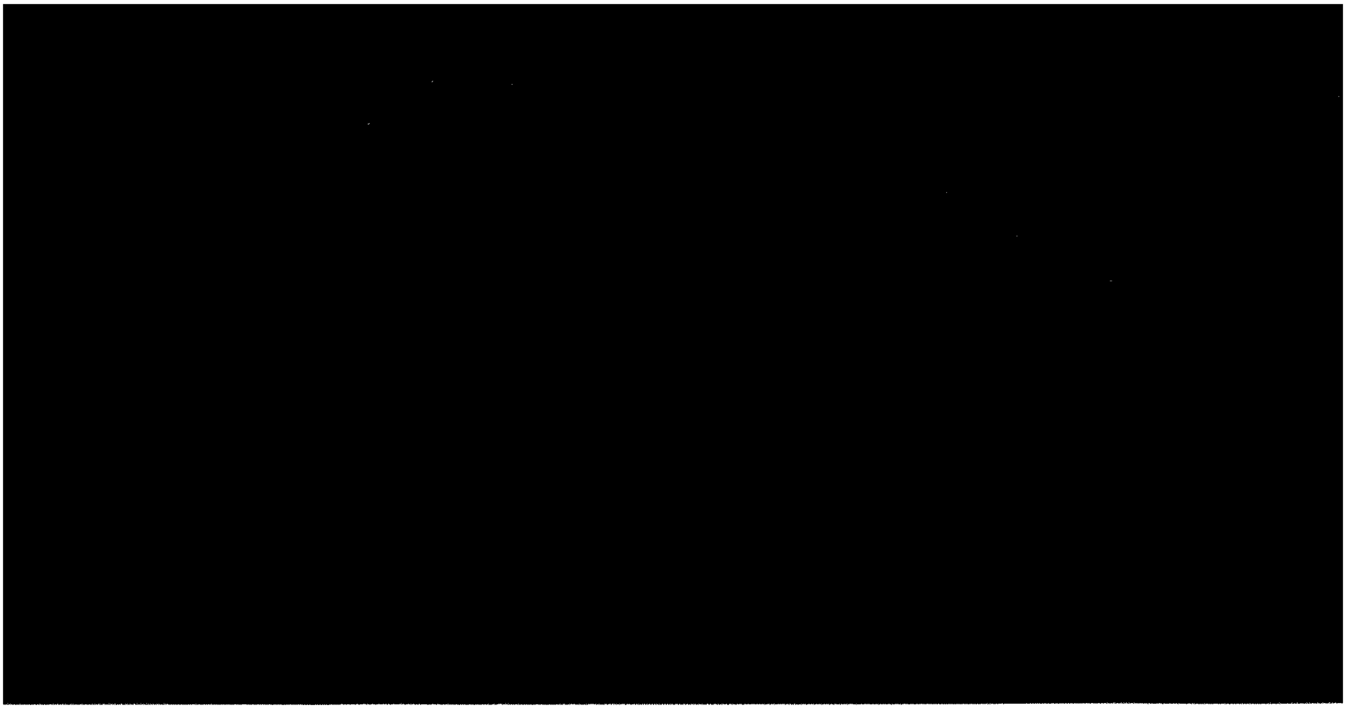
Dispersed 90-second processing utilizing the Kodak system enhances these benefits. There's no time-consuming transportation of bulky cassettes to and from central processing. Processed radiographs remain with the radiologist or technologist until the examination has been completed; finished films are not subject to misfiling or loss.

Hospital benefits

For the hospital radiologist and the radiologist in private office practice, the Kodak 90-second processing system means greater economy through greater staff efficiency. Also it means that examination facilities that seem to shrink day by day under increasing case loads can do the job without further expansion. In some cases, hospitals have reported that faster patient service through rapid film access has actually shortened patients' stays in the hospital. Dispersed installations further increase efficiency (examination-room occupancy time may be decreased by as much as 25 percent).

Benefits to the technologist

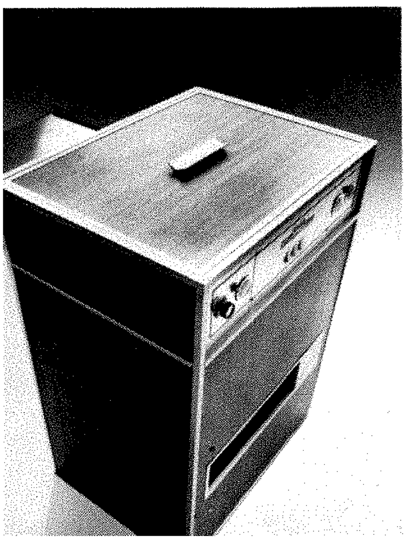
The technologist benefits, too, by being able to do his job more efficiently. For one thing, immediate film access



minimizes chances of misplacing or misfiling film. For another, quality improves when the technologist is able to check technic before the patient leaves the room. In this way, finished radiographs can be correlated with the technic used. This, of course, can prove most helpful in instructing students. Finally, there is no lost time resulting from the confusions of a processing backlog; films are processed as rapidly as exposed. Only $6\frac{1}{2}$ minutes are required to process a 20-film series of 14 x 14-inch radiographs in a *Kodak RP X-Omat* Processor, Model M6.

What about results?

Obviously, results are critical. One question most radiologists wanted answered before they converted to the Kodak 90-second processing system was: what about quality? Millions of sheets of film later, it has been confirmed that the *Kodak RP X-Omat* System is producing radiographs of high diagnostic readability time after time . . . and to the standard of quality you've come to expect from Kodak x-ray products. Additionally, because rapid processing permits immediate correlation of technic and results, quality improves still further. And for greater versatility, there are now three films from which to choose, depending upon the radiographic situation.



Changing to "90"

The compact *Kodak RP X-Omat* Processor, Model M6, is the first processor designed for 90-second processing. After a year and a half of use in private offices, clinics, and large hospital departments, it's proven to be the answer to today's and tomorrow's processing needs. It takes less than 5 square feet of floor space and so is ideally suited to a wide variety of installation situations without extensive renovations. Yet with its 60-inch-per-minute capacity it gives the faster service, smoother traffic flow, and new efficiency of the *Kodak RP X-Omat* System.

It pays to have a system

All elements of the *Kodak RP X-Omat* System—the new films, processor, and chemicals—have been carefully built by Kodak to work together. Optimum-quality radiographs are provided by use of these compatible products. It's the only fully integrated 90-second processing system in the world. By utilizing Kodak 90-second processing as a system, radiologist and technologist have an exact knowledge of what they are working with and how they can expect it to perform. Instead of variance, there's uniformity. The results? Dependable, predictable service day in, day out.

Learn how the *Kodak RP X-Omat* System can benefit your private office and hospital practice. Your Kodak Technical Sales Representative or *Kodak X-Omat* Dealer will be glad to discuss the benefits with you.

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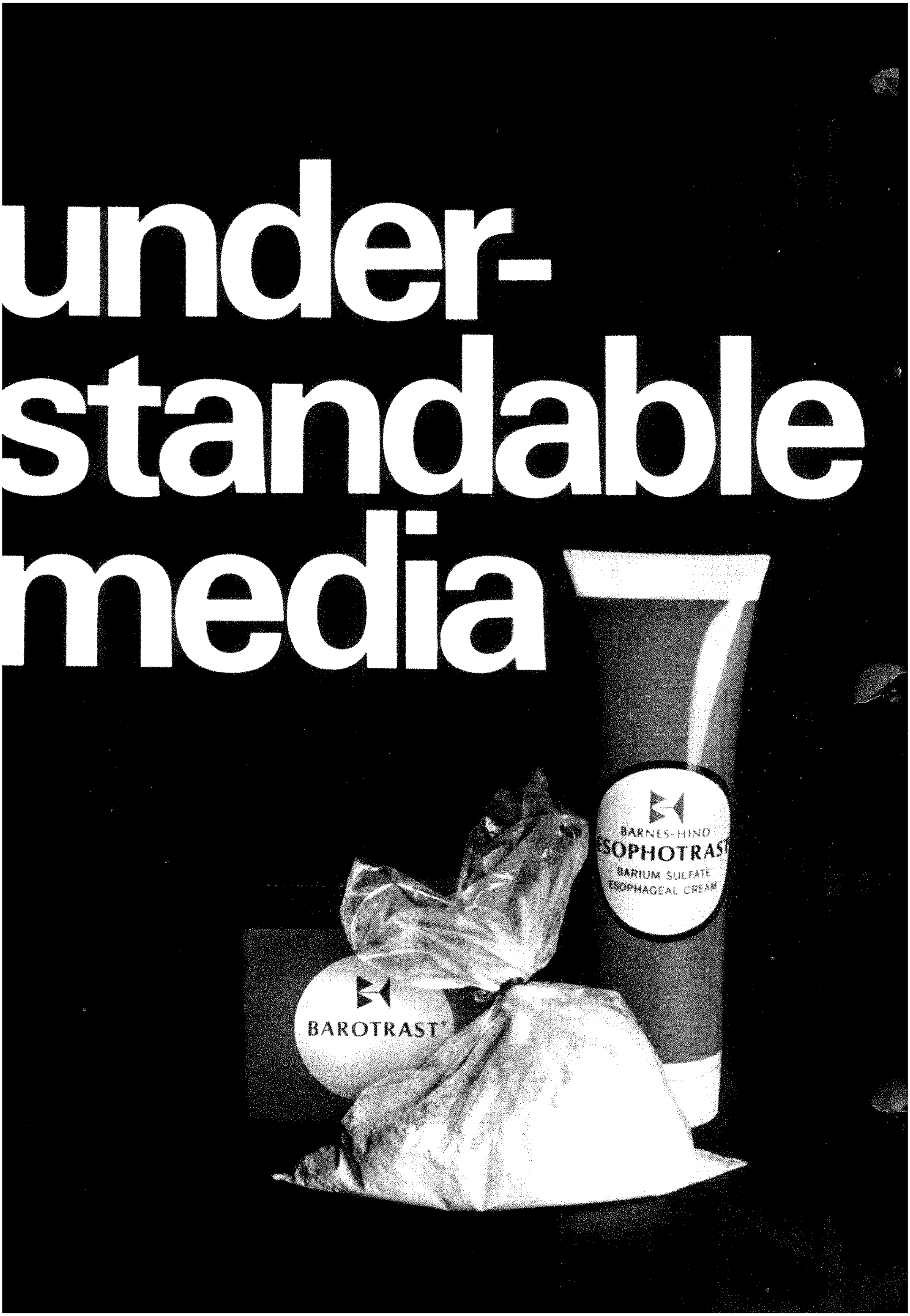
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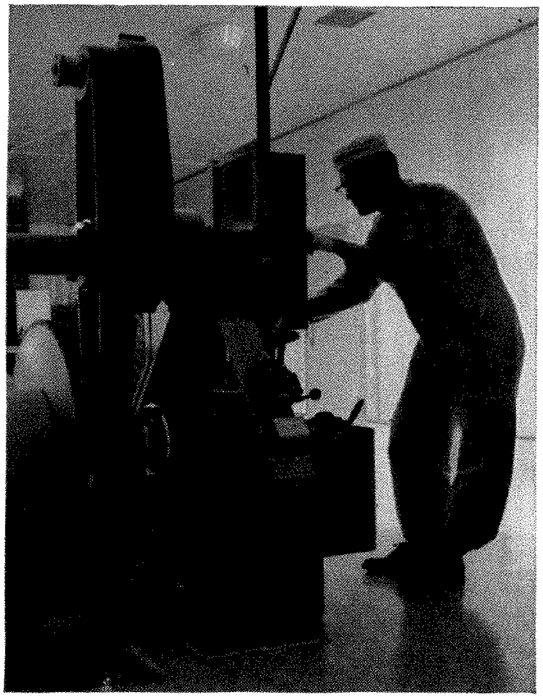

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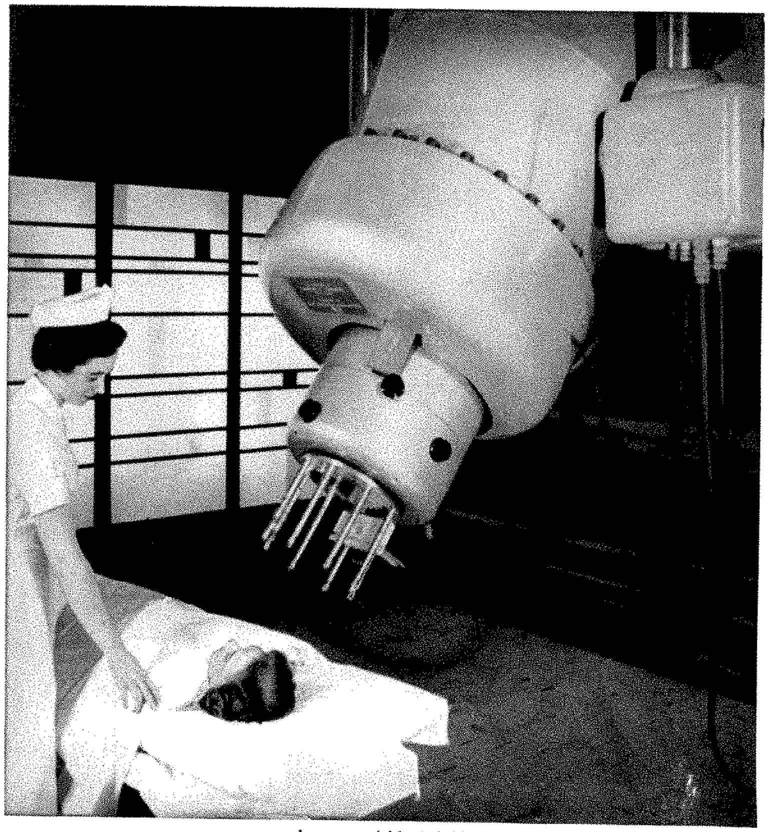

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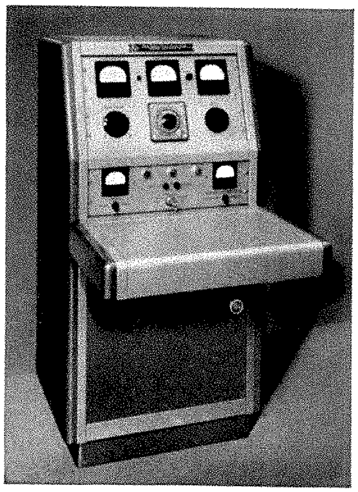

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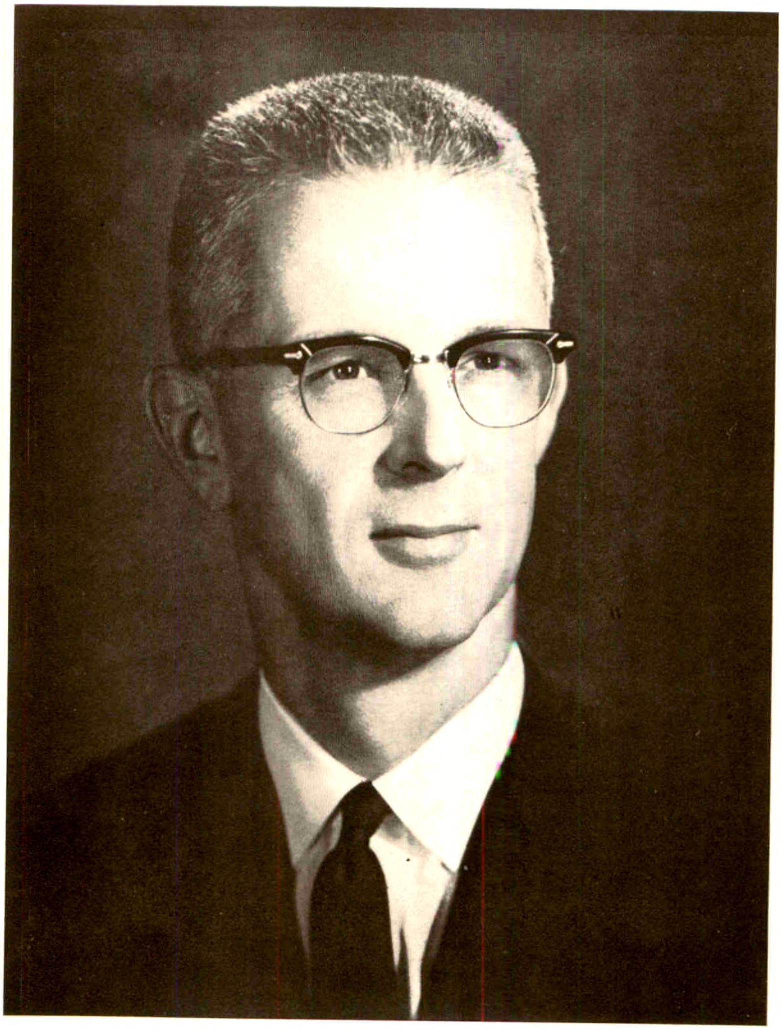

JOHN W. KIRKLIN, M.D.
Caldwell Lecturer, 1967

THE AMERICAN JOURNAL
OF ROENTGENOLOGY
RADIUM THERAPY AND
NUCLEAR MEDICINE

VOL. 102 FEBRUARY, 1968 No. 2

INTRODUCTION OF CALDWELL LECTURER, 1967

By ROBERT E. GROSS, M.D.
LADD PROFESSOR OF CHILDREN'S SURGERY, HARVARD MEDICAL SCHOOL
BOSTON, MASSACHUSETTS

We are honored this evening to have Dr. John Kirklin present the Caldwell Lecture and to receive the Gold Medal Award of the Society in recognition of his contributions to American Surgery.

In introducing the speaker, the first thing to note is a word about his father—Dr. Byrl R. Kirklin, who was a Professor in Radiology and Head of that Department at the Mayo Clinic. He was President of the American Roentgen Ray Society in 1937 and gave the Caldwell Lecture at the Annual Meeting in 1948. Therefore, young John is not only well qualified professionally to be our distinguished lecturer, but he is also qualified personally and sentimentally because of his father's eminence in Radiology and also in this Society.

Dr. Kirklin attended college at the University of Minnesota, from which he graduated in 1938, first in a large class, summa cum laude. *His medical education was at the Harvard Medical School; a review of comments made by course instructors through the four years generally described the student as "outstanding." Dr. Elliot Cutler, the Professor of Surgery, intensely interested through his whole professional life in the teaching of students, wrote down at the time that "this is the brightest medical student I have ever encountered." An annual prize had been established in the school in honor of Dr. Henry Christian, to be given "to the fourth year student who has displayed diligence and notable scholarship in his studies and offers great promise for the future." This award was given to Kirklin on Dr. Christian's birthday in February, 1942. In that year he was graduated, the first man in his class of 150, and was given an M.D. degree* magna cum laude.

The years from 1942 through 1949 were filled with various appointments giving him general surgical training and fulfillment of military obligations.

In 1950 he was appointed to the active staff of the Mayo Clinic, and ever since has made an amazing number of important contributions to the field of surgery. We can summarize his work very well from a study of his publications because he has been a most prolific writer and has put forth some three hundred articles. It is astounding to see the great diversity of conditions—more than forty—which have held his attention. In the last twelve years his efforts have been concentrated in the field of cardiovascular surgery. There have been forty-seven articles re-

garding extracorporeal circulation, apparatus for conducting it, and methods for controlling it in such a way as to minimize alterations in humans for whom this technique is employed. There have been twenty-one contributions regarding mitral stenosis and insufficiency and eighteen more on various lesions of the aortic valve. He is particularly well known for one hundred contributions relating to various aspects of surgical treatment of congenital heart disease.

It is obvious that Dr. Kirklin has not restricted himself to the technical aspects of surgery. One finds a strong attention to pathologic anatomy and where previously this had been vague, there have been appropriate studies to clarify anatomic knowledge. One finds that the man has given much thought to elucidation and control of physiologic disturbances in several of the cardiovascular conditions. It has been obvious that there is a striking background from the experimental laboratory, to devise or test new surgical approaches when there is need for these. It is surprising to find how often roentgenologic aspects of many of the cardiovascular anomalies have been pointed out by him as important guides for the surgeon. It is a measure of the honesty and objectivity of the man to see the numerous papers giving evaluations of short and long-term results of surgical repairs. Dr. Kirklin's writings are succinct, lucid, informative, and authoritative. Undoubtedly, many of them will become classics. Not a few of the contributions are among the great surgical advances in our generation. It is fully evident that to develop and perform these techniques—and to teach them to others—are the marks of a great master.

Dr. Kirklin belongs to some twenty professional societies, is a member of five editorial boards, The American Board of Surgery, the National Board of Medical Examiners, and is on the Surgical Study Section of the National Institute of Health. He has been given an honorary Doctorate of Medicine and also one of Science.

Dr. Kirklin was a most prominent member of the Mayo Clinic Surgical Staff from 1950 to 1966, and for the last year has been Professor and Chairman of the Department of Surgery at the University of Alabama.

It is a real pleasure to present Dr. John Kirklin, who is widely regarded as the Dean of American Surgery today.

Vol. 102, No. 2

THE TETRALOGY OF FALLOT*

CALDWELL LECTURE, 1967

By JOHN W. KIRKLIN, M.D.
BIRMINGHAM, ALABAMA

President Good did me a very great honor when he asked me to be the forty-seventh Caldwell Lecturer. Those who have previously delivered this oration have been radiologists, scientists, surgeons, or educators. I consider myself to be an individual, presented in my lifetime with the most magnificent opportunities any man could have wished for. I hope to tell you tonight about some of the knowledge that grew out of those opportunities.

First, please allow me a few asides. In the fall of 1939, when I was in my second year at the Harvard Medical School, I heard a lecture on wound healing delivered by a young surgeon named Robert E. Gross. Only a short time before, he had become the first man successfully to close a patent ductus arteriosus. When he delivered that lecture, he looked the same as he looks tonight. If you observe him closely, you see, as I saw nearly 30 years ago, the sturdy, yet sensitive hands of a skilled craftsman, the calm, appraising eye of an intelligent and cool observer, the demeanor of a scientist, and the charm of an artist. I decided at that moment in 1939 that I would try to emulate this man. One day in 1945, while in the Army, I read an article by Gross and Hufnagel describing for the first time the repair of coarctation of the aorta. There followed a succession of brilliant triumphs by Dr. Gross that have established him as one of the very few surgical geniuses of our time. In 1948 I spent 6 months with him again, and my own surgical techniques and practices still reflect what I learned in those months. Whatever skill I possess as a surgeon is the result of my education by Robert E. Gross, and three other men, my respected friend Jim Clagett, Dr. Stuart W. Harrington, and Dr. Francis Murphey of Memphis, Tennessee, with whom I worked as a neurosurgeon in World War II. These men passed on to me their enormous knowledge and their magnificent surgical techniques. This has been a priceless heritage, one which I have treasured and one which I am endeavoring to pass on to my young colleagues, residents, and students.

My father was a radiologist and delivered the Caldwell Lecture in 1948. The giants of radiology of the 1930's were well known to me as a young man, and I admired and respected them. I was particularly impressed with the high regard they had one for another, and their loyalty to each other and to their specialty.

It has been my privilege to know President Good since I was a young man. Dr. Good quickly established himself as an outstanding radiologist, and through the years he has contributed in a remarkable fashion to his specialty. I respect him for that, and I am therefore particularly honored that he asked me to deliver this lecture.

Radiologists have been kind to me throughout my career and continue to play an important part in my professional activities. Drs. Owings Kincaid and George Davis and I learned many things together while I was at the Mayo Clinic, and they were generous in allowing me to use for this lecture tonight some of the material we developed together. Dr. Alberto Barcia, who has been teaching me for years, and who is now a member of the Department of Radiology at the University of Alabama Medical Center, and his colleague in Alabama, Dr. Lester Glover, have been generous in their help to me in my new environment in Alabama and I look forward to exploring new fields with them in the future.

MORPHOLOGY AND ANGIOCARDIOGRAPHY

Certain anatomic landmarks can be recognized within the normal right ventricle, and it is distortions of these that result in

* Presented at the Sixty-eighth Annual Meeting of the American Roentgen Ray Society, Washington, D. C., September 26–29, 1967.
From the Department of Surgery, University of Alabama Medical Center and the Veteran's Administration Hospital, Birmingham, Alabama.

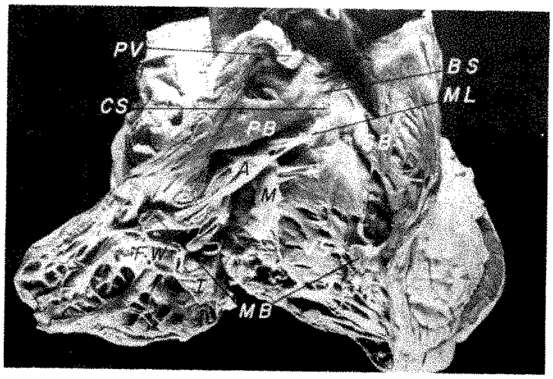

Fig. 1. In this specimen from a normal subject, the anterior wall of the right ventricle has been incised to the right of the left anterior descending artery and hinged back to the right. PV = Pulmonary Valve. CS = Crista Supraventricularis. VS = Ventricular Septum. SB = Septal Band. MB = Moderator Band. PB = Parietal Band. (Reproduced with permission from Drs. Van Pragh and Ongley. Anatomic types of single or common ventricle in man. *Am. J. Cardiology*, 1964, *13*, 367–386.)

tetralogy of Fallot (Fig. 1). The tricuspid valve empties into the inflow portion of the right ventricle, and the pulmonary valve is at the exit from the right ventricle. The crista supraventricularis is just cephalad to the inflow portion of the ventricular septum. The septal band and its extension, the moderator band, extend to the left and down from the crista supraventricularis. The parietal band extends to the right and down from the crista. Some chordae of the tricuspid valve insert into the papillary muscle of the conus (or medial papillary muscle) which is just upstream to the crista.

With this introduction of terms, we can now define the specific entity called the *tetralogy of Fallot.* We now agree with Van Mierop and others that it is a unique combination of intracardiac defects. These include a large ventricular septal defect which is immediately beneath the aortic valve but slightly more anterior than the usual isolated defect in the ventricular septum. The aorta is dextraposed, and arises to a variable degree from the right as well as the left ventricle. There is a functionally unimportant minor malformation of the tricuspid valve and an absence of the medial papillary muscle (or papillary muscle of the conus). There is stenosis of the ostium infundibulum, which alone or associated with additional narrowing downstream to this area offers sufficient resistance to blood flow to result in essentially equal peak systolic pressures in the two ventricles. It is said that tetralogy of Fallot results basically from anterior and upward displacement of the conus septum during embryologic development.

The ostium infundibulum is produced by hypertrophy and anterior displacement of the crista supraventricularis. The parietal band (derived from the conus septum) and the septal band are usually hypertrophied and produce additional narrowing at and/or just upstream to the ostium infundibulum. Between the ostium infundibulum and the pulmonary valve is the variable-sized infundibular chamber (Fig. 2). The orifice of the pulmonary valve, which may or may not be narrowed, is a little downstream to the attachment of the base of the cusps

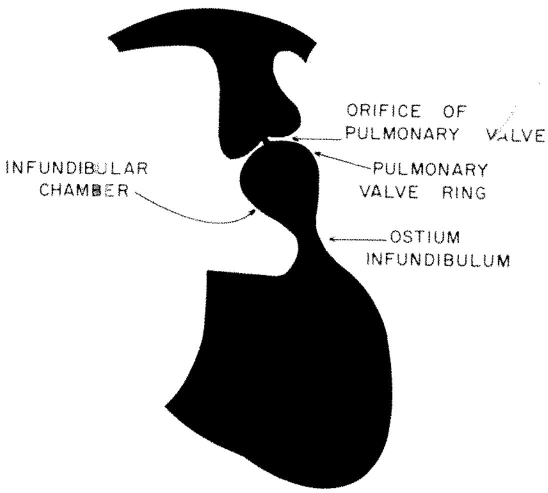

Fig. 2. Schematic representation of right ventricle and pulmonary artery as seen angiographically in patients with tetralogy of Fallot. (Modified from Kincaid: Angiocardiography in obstructive malformations of the right ventricle and pulmonary arteries. In: Progress in Angiocardiography. Charles C Thomas, Publisher, Springfield, Ill.)

of this valve to the junctional area between the artery and right ventricle. The level of basal attachment of the cusps is termed the pulmonary valve ring. The cusps are also attached at their commissures to the wall of the pulmonary artery. A localized stenosis of this area of the main pulmonary artery may result from shortening of the free edge of these cusps.

A clinically severe syndrome of cyanosis, polycythemia, and symptoms may result from any type of morphology, as will be seen later, and thus clinical severity is not directly related to morphology. However, the ease of operation *is* related to morphology, particularly that of the pulmonary stenosis, and this must be examined in some detail. Right ventricular outflow resistance may be localized at the ostium infundibulum (Fig. 3; and 4). In some patients there is an additional significant resistance to flow at the stenotic ostium or orifice of the bicuspid pulmonary valve (Fig. 5, *A* and *B*). In others, the stenosis

Fig. 3. (This and subsequent angiocardiograms are from patients with tetralogy of Fallot. Unless otherwise indicated, injection is into the right ventricle.) At operation in this patient the ostium infundibulum was found to be narrow because of hypertrophy and anterior displacement of parietal band and crista supraventricularis and some hypertrophy of the septal band. Infundibular chamber was well developed. Pulmonary valve was bicuspid but not stenotic, although it appears here to be domed.

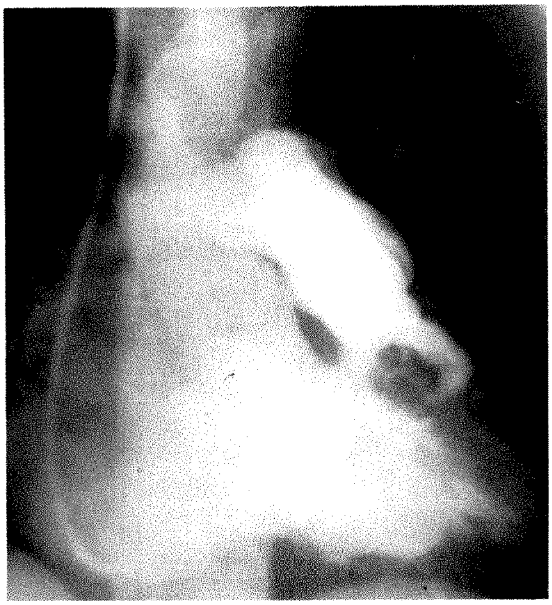

Fig. 4. Severe stenosis of ostium infundibulum exists because of massive hypertrophy of septal band and hypertrophy and anterior displacement of parietal band. Infundibular chamber is wide. Pulmonary valve is bicuspid but not stenotic. Note recess above and lateral to septal band.

at the ostium infundibulum is mild, and that at the orifice of the valve severe (Fig. 6, *A* and *B*). The infundibular chamber itself is narrow in some patients with stenosis of the ostium infundibulum or valvular orifice (Fig. 7, *A* and *B*). Very occasionally, there is also a marked, localized narrowing of the main pulmonary artery, the mechanism of which has been mentioned earlier. The origin of the right or left pulmonary artery may be the site of a localized stenosis in a few patients with tetralogy of Fallot, and such a stenosis can produce significant resistance to flow (Fig. 8). Rarely, the main pulmonary artery and right and left pulmonary arteries are diffusely narrow (Fig. 9).

Occasionally, the left pulmonary artery is absent in tetralogy of Fallot (Fig. 10). Careful study by properly programmed angiocardiography is necessary before it can be concluded that the artery is absent rather than very small. Absence of the right pulmonary artery has not been re-

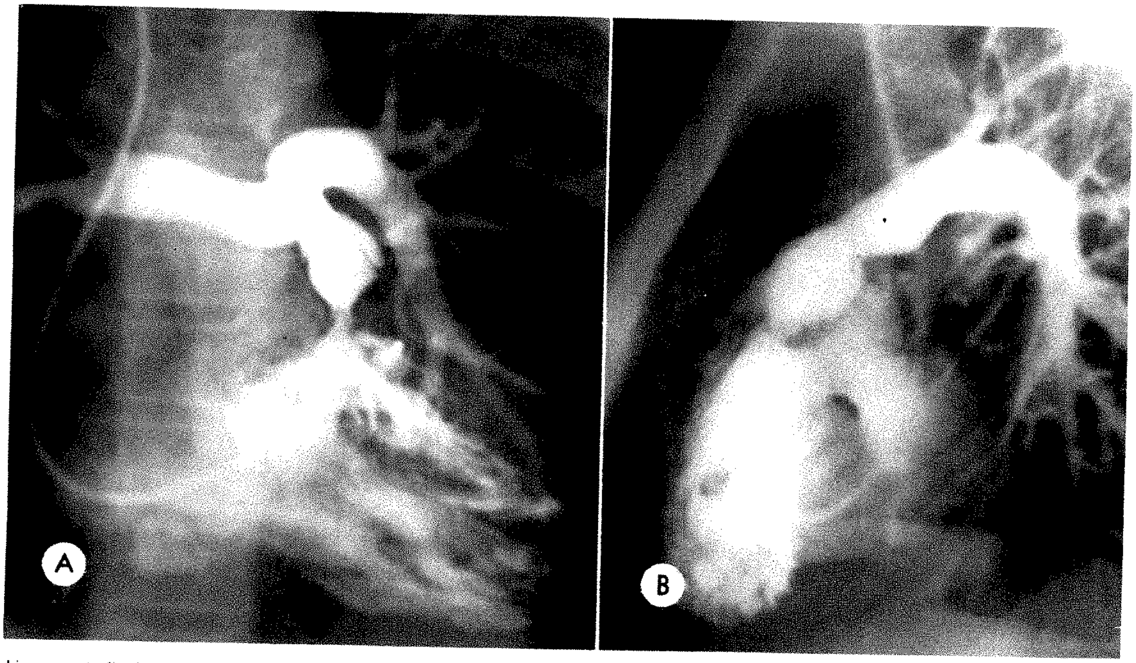

Fig. 5. (A) Anteroposterior and (B) lateral angiocardiograms. At surgery, in addition to severe stenosis at ostium infundibulum, there was found severe valvular stenosis. The pulmonary valve is domed in the angiocardiogram, but appears similar to the valve in Figure 3, which at operation was found not to be stenotic. The infundibular chamber and pulmonary valve ring are of adequate size.

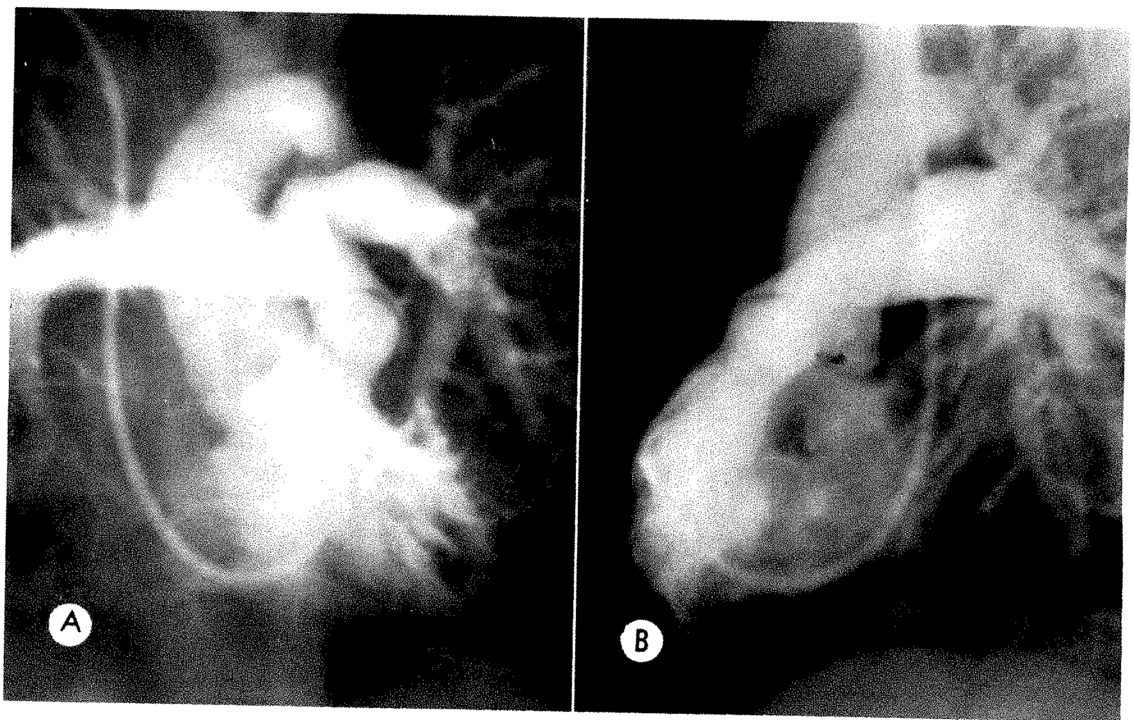

Fig. 6. (A) Anteroposterior and (B) lateral angiocardiograms. This patient had only mild stenosis of the ostium infundibulum, a wide infundibular chamber and pulmonary valve ring, but severe stenosis of the orifice of the pulmonary valve.

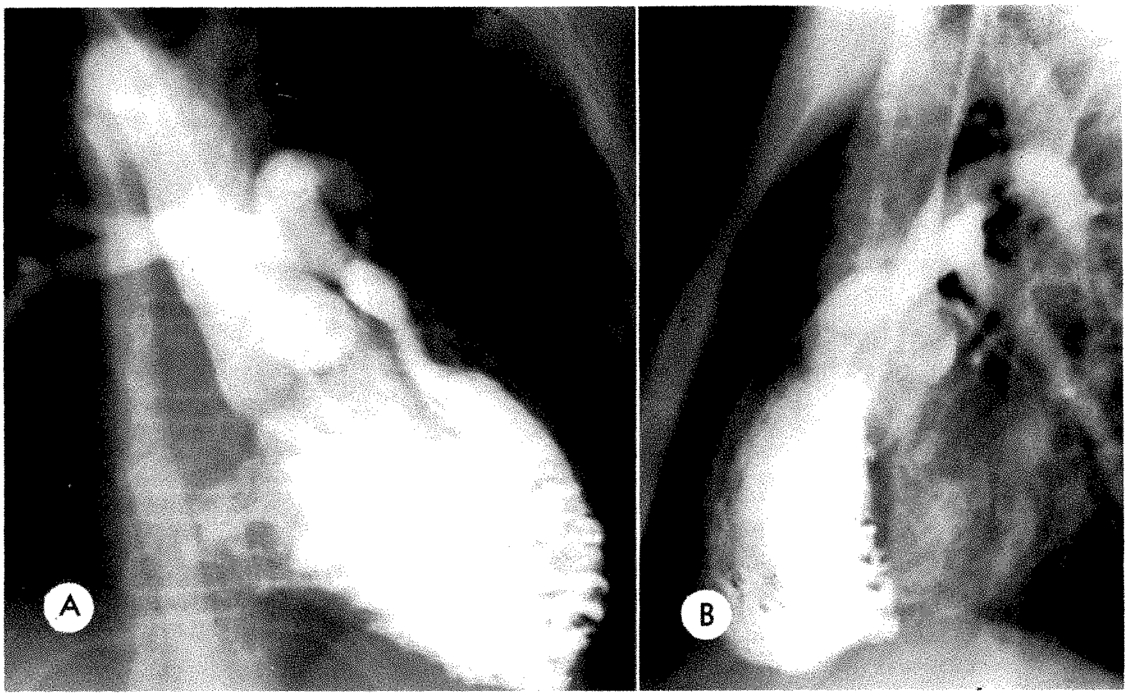

FIG. 7. (*A*) Anteroposterior and (*B*) lateral angiocardiograms. The ostium infundibulum is moderately stenotic, but right ventricular output resistance is severely elevated because of the long, narrow infundibular chamber. At surgery, the pulmonary valve was found to be severely stenotic. Intracardiac repair was successfully accomplished without a patch being placed in the outflow tract, and immediately after repair peak pressure in right ventricle was 70 mm. Hg and in the left 85 mm. Hg.

ported to occur in tetralogy of Fallot. Infrequently, the left or right pulmonary artery originates from the aorta in a patient with otherwise typical tetralogy of Fallot (Fig. 11, *A* and *B*; and 12, *A* and *B*).

The morphology of tetralogy of Fallot, as well as the physiology, can become altered after an anastomotic operation such as the Blalock-Taussig procedure. In most

FIG. 8. In this patient there was also localized stenosis at origin of right pulmonary artery.

FIG. 9. The main, right and left pulmonary arteries are very narrow.

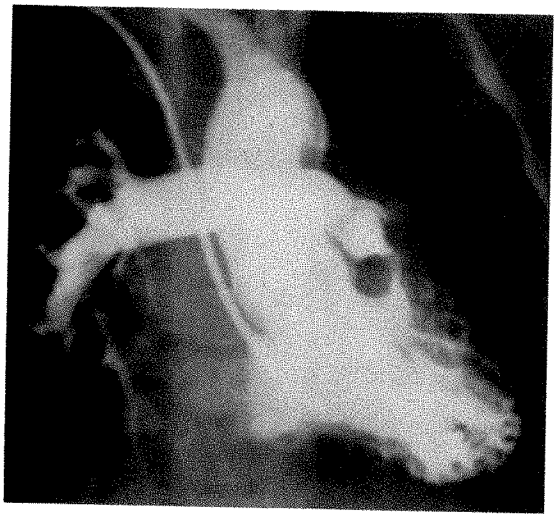

FIG. 10. There is complete absence of the left main pulmonary artery in this patient.

patients with the tetralogy of Fallot, the pulmonary stenosis becomes more severe as time passes because of the increasing hypertrophy of the crista and parietal and septal bands. When the patient is kept alive beyond his time, so to speak, by a Blalock-Taussig operation, there is an unusually long time of increasing hypertrophy allowed. Thus in some patients a near atresia of the ostium infundibulum develops in the years after a Blalock-Taussig operation has been performed (Fig. 13). Of course, an enormous collateral arterial circulation develops also, because of the interruption of the subclavian artery incident to the Blalock-Taussig operation (Fig. 14).

HEMODYNAMICS

Characteristically, patients with tetralogy of Fallot have a right-to-left shunt. Venous blood passes from the right ventricle into the systemic circulation, resulting in cyanosis. In a few patients, the shunt is bidirectional and of about equal magnitude in the two directions. In a few it is dominantly left-to-right and these patients are not cyanosed.

The severity of the pulmonary stenosis seems to be the major determinate of the hemodynamic state and thus of the clinical syndrome in patients with tetralogy of Fallot. When the stenosis is severe, the shunt is right-to-left and is large, and the patient is deeply cyanosed, severely polycythemic, and profoundly disabled. When the pulmonary stenosis is less severe, the magnitude of the right-to-left shunt and degree of cyanosis are less. Where the pulmonary stenosis is only moderate, the shunt is bidirectional and the patient mildly cyanotic or indeed acyanotic. Thus, in general, the relationship between the output resistance of the two ventricles, de-

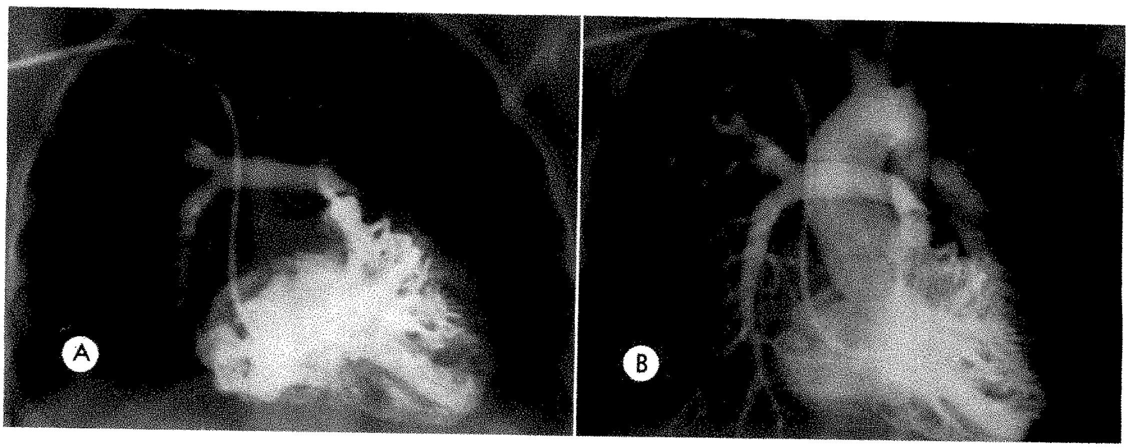

FIG. 11. (*A*) The left pulmonary artery originates from the aorta, probably by way of patent ductus arteriosus. (*B*) Complete repair, including disconnection of left pulmonary artery from aorta and implantation of it onto main pulmonary artery, was effected by Dr. D. C. McGoon. (Reproduced with permission from Drs. Stewart, Kincaid, and Edwards. An Atlas of Vascular Rings and Related Malformations of the Aortic Arch System. Charles C Thomas, Publisher, Springfield, Ill., 1964.)

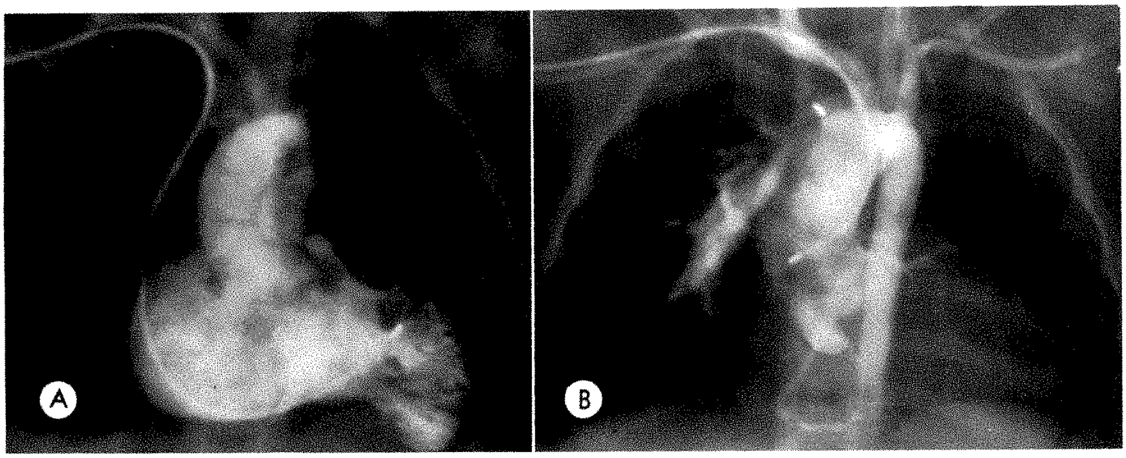

FIG. 12. (*A*) Right ventriculogram. (*B*) Aortogram. This patient with tetralogy of Fallot has a right pulmonary artery which originates from the ascending aorta. Complete repair is planned in the future. (Reproduced with permission from Drs. Ongley, Rahimtoola, Kincaid, and Kirklin. Continuous murmurs in tetralogy of Fallot and pulmonary atresia with ventricular septal defect. *Am. J. Cardiology*, 1966, *18*, 821–826.)

termined largely by the severity of the pulmonary stenosis, dictates the hemodynamic state.

Recent studies from Duke University Medical Center, while in no way invalidating this concept, indicate that the details of

FIG. 13. There is only a very narrow channel through the ostium infundibulum (left subclavian-pulmonary artery anastomosis had been performed previously). The infundibular chamber, pulmonary valve ring and orifice were all found adequately wide at operation. (Reproduced with permission from Drs. Ongley, Rahimtoola, Kincaid, and Kirklin. Continuous murmurs in tetralogy of Fallot and pulmonary atresia with ventricular septal defect. *Am. J. Cardiology*, 1966, *18*, 821–826.)

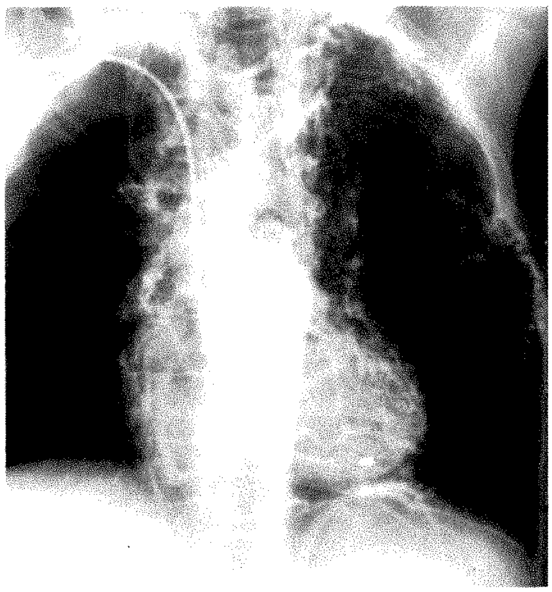

FIG. 14. This frame, exposed late after right ventricular injection, demonstrates the enormous collateral arterial circulation developing after interruption of the left subclavian artery. (Reproduced with permission from Drs. Ongley, Rahimtoola, Kincaid, and Kirklin. Continuous murmurs in tetralogy of Fallot and pulmonary atresia with ventricular septal defect. *Am. J. Cardiology*, 1966, *18*, 821–826.)

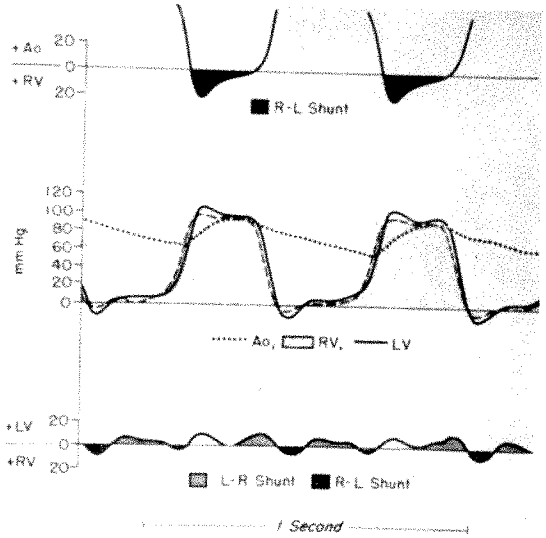

Fig. 15. Studies in a patient with severe tetralogy of Fallot. *Top:* Aortic-right ventricular pressure gradient. *Middle:* Simultaneous right and left ventricular and aortic pressures. *Bottom:* Pressure gradient and direction of flow across the ventricular septal defect. (Reproduced with permission from Drs. Levin, Boineau, Spach, Canent, Capp, and Anderson. Ventricular pressure-flow dynamics in tetralogy of Fallot. *Circulation*, 1966, *34*, 4–13.)

the movement of blood between the two ventricles and aorta in tetralogy of Fallot are complex. They have shown that the rise and fall of pressure in the right and left ventricle during the cardiac cycle is asynchronous in these patients. The movement of blood across the ventricular septal defect and into the aorta at any moment in the cardiac cycle is determined by the pressure gradient between the two ventricles and between them and the aorta at the moment (Fig. 15). The determinants of these pressure gradients are many and complex.

A collateral circulation to the lungs usually develops in cyanotic patients with the tetralogy of Fallot, and at times it may be so large that the clinical syndrome is majorly affected by it. This has been termed by some the "bronchial circulation," but the term aorticopulmonary collateral circulation seems more appropriate since these vessels originate from many sources, including the aortic arch, the descending thoracic aorta and its branches, and at times the abdominal aorta. Gas exchange has been shown to be augmented by this circulation, and it therefore delivers blood to the pulmonary capillaries. As much as 50 per cent of the aortic blood flow may run off to the lungs by way of these collateral vessels in pulmonary atresia with absent pulmonary arteries (Fig. 16). The magnitude of the aorticopulmonary collateral circulation in patients with tetralogy of Fallot has been reported to range from 5 per cent to 30 per cent of the systemic blood flow. Unusual cases of tetralogy of Fallot have been observed in which these collateral channels and the flow through them have been so large that a continuous murmur was heard, and the oxygen saturation of blood in the pulmonary artery was above 90 per cent. Because of these large, naturally occurring systemic-pulmonary artery shunts, such patients may be only minimally cyanotic, in spite of severe pulmonary stenosis.

LIFE HISTORY

Infants with tetralogy of Fallot can die during an acute hypoxic episode. These are believed to result from acute powerful con-

Fig. 16. Aortogram in a patient with ventricular septal defect, pulmonary atresia, and absent pulmonary arteries. Enormous aorticopulmonary collateral vessels are demonstrated.

traction of the muscular components of the ostium infundibulum resulting in acute increase in severity of the pulmonary stenosis and acute decrease in pulmonary blood flow. Some infants born with little or no cyanosis do not begin to develop significant symptoms until the age of 2, 3 or 4 years. Such patients are usually severely disabled by the age of about 8 years and when surgery was not available, they frequently died in their early teens. Their course is characterized by increasing cyanosis, exercise intolerance, squatting, and polycythemia, resulting from increasing severity of the pulmonary stenosis and consequent increasing right-to-left shunt.

Accidents may occur to change abruptly the course in a given patient. Massive hemoptysis can occur, presumably from rupture into the lung of large aorticopulmonary collateral channels. Cerebral infarction, with or without abscess formation, can result in hemiplegia or death. Intracardiac right-to-left shunting of contaminants in venous blood, hypoxemia, polycythemia, increased apparent viscosity of the blood and consequent thrombosis in cerebral vessels, all play a role in inciting this catastrophe.

INDICATIONS FOR OPERATION

The need for intracardiac surgical repair in patients with tetralogy of Fallot is clear. The ideal age for the operation, we believe, is about 5 or 6 years, and when we see children younger than this who are getting along reasonably well, we usually defer operation until then. There is no reason to defer it beyond this age.

At times the severity of the symptoms necessitates operative intervention prior to the ideal age for intracardiac repair. Although we and others have performed, for one reason or another, intracardiac repair in children 2 or 3 years of age with good success, I continue to believe that the risk in this must be a little higher than desirable. Thus, if surgical intervention becomes necessary before the age of about 5 years, we usually perform a palliative operation. Intracardiac repair is then done at about 5 or 6 years of age, even though good palliation continues. In general, the palliative operation of choice is the Blalock-Taussig operation of end-to-side subclavian-pulmonary artery anastomosis. Under a few special circumstances other operations are preferable.

INTRACARDIAC REPAIR

Closure of the ventricular septal defect and relief of the pulmonary stenosis are the basic features of intracardiac repair. Partial resection of the crista supraventricularis, the parietal band, and the septal band, and mobilization of the anterior or free wall of the right ventricle from these bands provide relief of the infundibular stenosis. Further room is provided for the outflow tract by pulling the cristal remnant dorsally or posteriorly, in the process of repairing the ventricular septal defect by using a teflon or dacron patch that is a little smaller than the actual defect (Fig. 17, *A*, *B* and *C*; and 18, *A* and *B*).

In about 15 per cent of the patients, the pulmonary valve ring and infundibular chamber, and at times the main pulmonary artery, are too narrow to allow adequate relief of the pulmonary stenosis by the methods just described. Since it is often difficult to assess the adequacy of repair visually, we nearly always now close the heart, discontinue cardiopulmonary bypass, and measure intracardiac pressures before deciding to insert a patch of pericardium for enlargement of the area. If peak systolic pressure in the right ventricle is the same or greater than that in the left, we usually re-establish perfusion and insert the patch. If right ventricular pressure is less than left, we do not. This policy has led to better early and late results than more liberal use of patches such as we practiced some years ago.

When previously a Blalock-Taussig operation has been performed, the shunt must be dissected out and closed before establishing cardiopulmonary bypass. Proper attention to technical details of the dissection

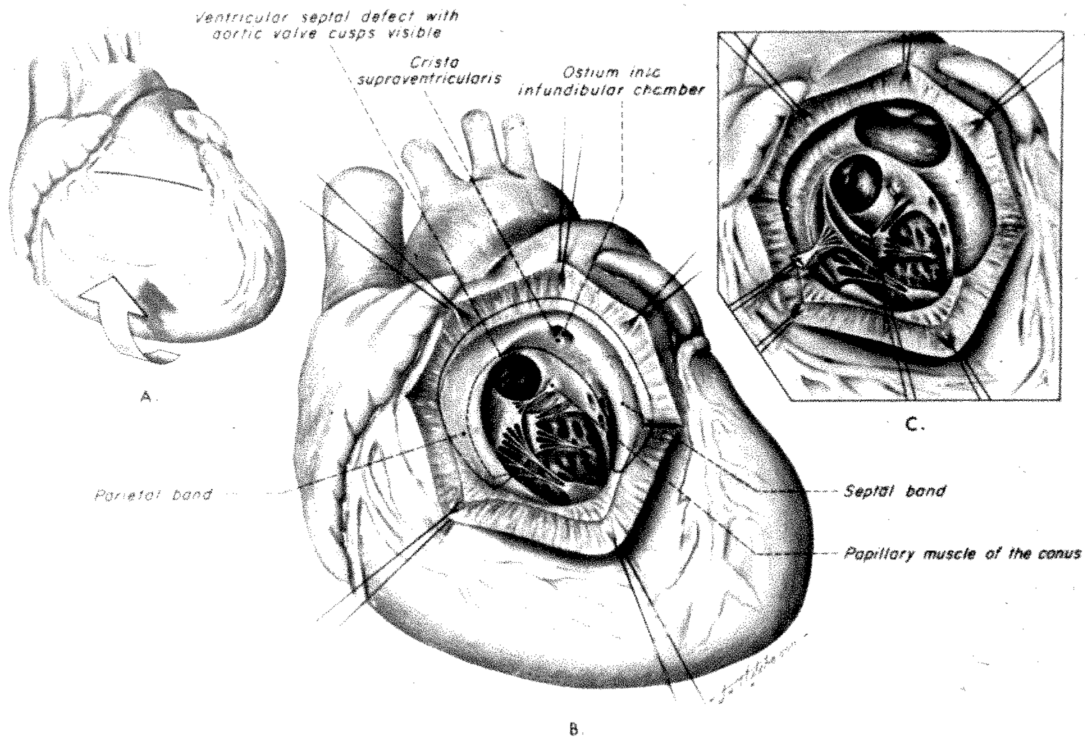

FIG. 17. (*A*) A transverse incision is made in the right ventricle. (*B*) Details of morphology within the right ventricle in tetralogy of Fallot. The lines encircle the tissue to be removed in relieving the infundibular stenosis. (*C*) Appearance after resection of this tissue.

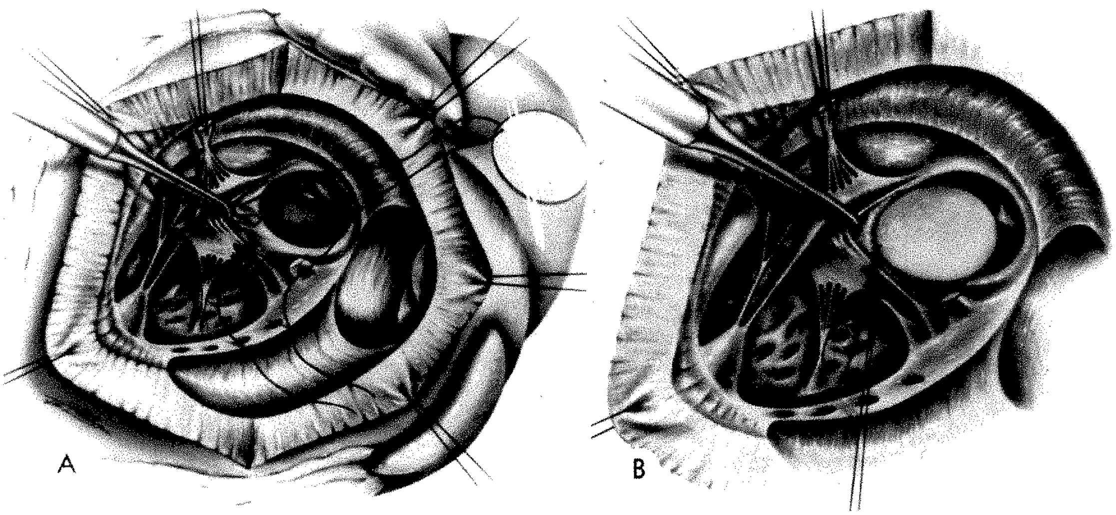

FIG. 18. (*A*) The first stitch has been placed for insertion of the patch to close the ventricular septal defect. (*B*) This stitch has been tied. Interrupted sutures are now placed between septum and right edge of patch, keeping the stitches away from free edge of septum in order to avoid producing heart block. The remainder of the suture line between patch and edges of the defect is made with interrupted sutures.

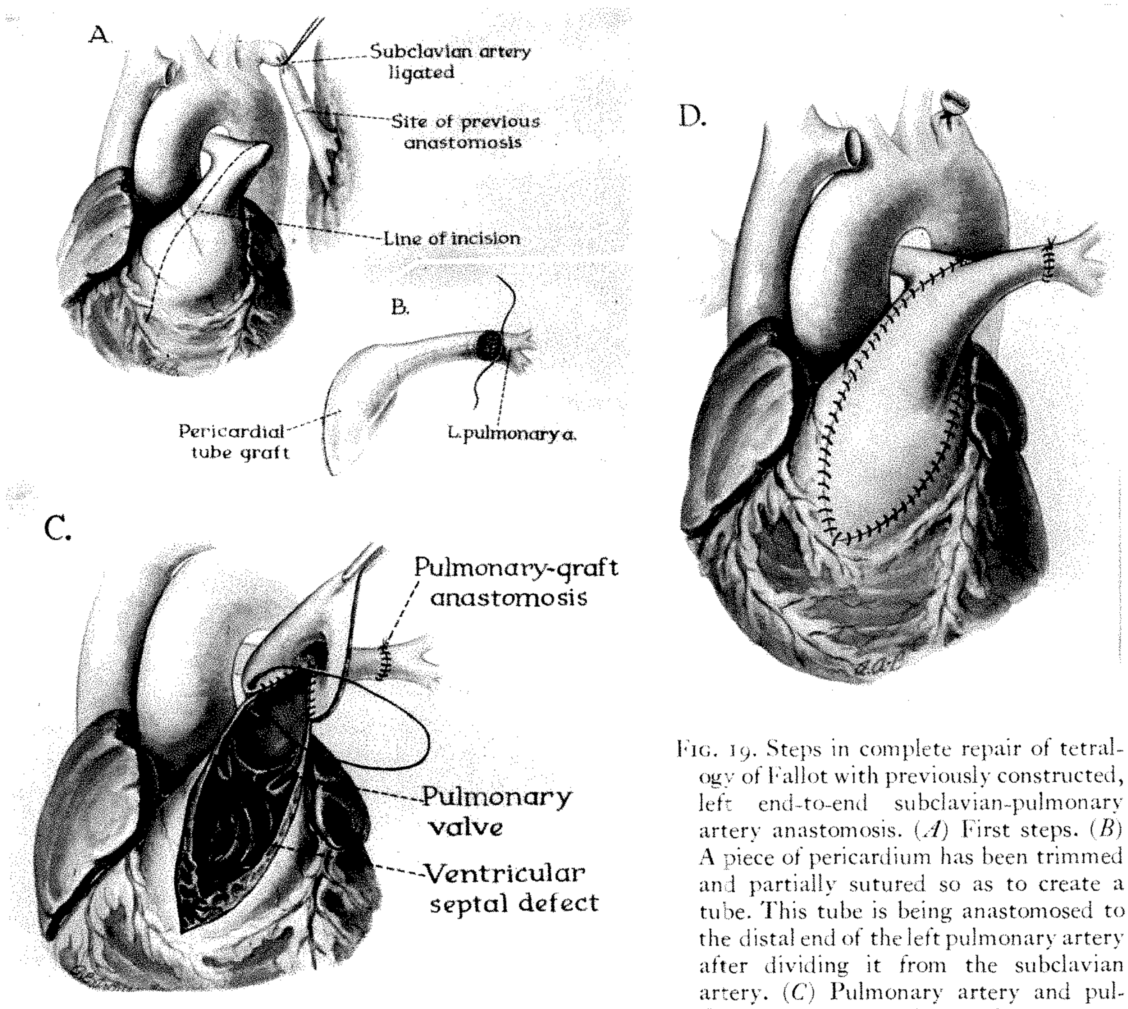

Fig. 19. Steps in complete repair of tetralogy of Fallot with previously constructed, left end-to-end subclavian-pulmonary artery anastomosis. (*A*) First steps. (*B*) A piece of pericardium has been trimmed and partially sutured so as to create a tube. This tube is being anastomosed to the distal end of the left pulmonary artery after dividing it from the subclavian artery. (*C*) Pulmonary artery and pulmonary valve ring are being enlarged with pericardial patch. (*D*) Completed intracardiac repair and reconstruction of flow to left lung.

allows this to be done safely, and without increased risk. When a previous Potts' anastomosis has been performed, external dissection of the area of anastomosis is difficult and closure of the anastomosis is best done from within the pulmonary artery during total circulatory arrest, while the patient's body temperature is about 23° C.

Occasionally an end-to-end type of Blalock anastomosis has been made between the subclavian and pulmonary artery, after disconnection of the pulmonary artery from the main pulmonary artery. Obviously, merely ligating the end-to-end Blalock anastomosis and performing intracardiac repair results in pulmonary blood flow going only to the lung on the side opposite that on which the Blalock operation was done. In our small experience with doing just this, the results have not generally been satisfactory. Therefore in recent years we have always reconstructed pulmonary flow, preferably by use of an autogenous pericardial graft (Fig. 19, *A–D*).

These intracardiac operations require cardiopulmonary bypass with the aid of a pump-oxygenator. The development of this technique, and the details of its application to this operation, are beyond the scope of this presentation. A few comments are

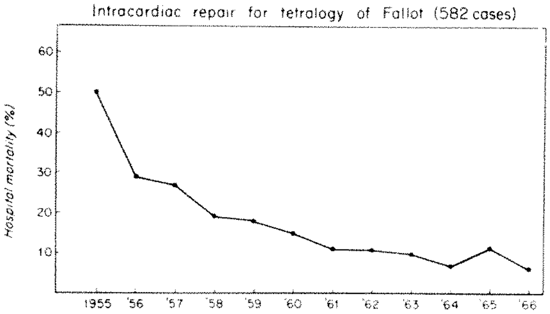

FIG. 20. Hospital mortality rate according to years. Operations in years 1955 through 1965 were at the Mayo Clinic. Operations in 1966 were in part at the Mayo Clinic and in part at the University of Alabama Medical Center.

nontheless pertinent. Intracardiac repair of tetralogy of Fallot is, in my opinion, a difficult operation. Success with it demands that it be done with precision. Thus 60 to 100 minutes of cardiopulmonary bypass may be required. This means that the perfusion of the patient from the pump-oxygenator must be as perfect as possible. Care must be taken, by methods which we shall not describe, to preserve particularly cardiac function, pulmonary function and renal function during this complex operative procedure. Although cardiopulmonary bypass allows us to do this operation safely under the conditions we have described, it is not as yet a perfect technique. Thus we and others are today actively investigating ways of improving this basic method of cardiovascular surgery.

POSTOPERATIVE CARE

The patient with heart disease, before and early after operation, often has significant derangements in organ function and in body composition. The challenge to us as surgeons is to understand these and to escort the patient safely through operation and the postoperative period by proper use of this knowledge. Our own research efforts in the past few years and at present are focused upon organ and system function in such patients before and after operation.

For example, early after intracardiac repair of tetralogy of Fallot cardiac output may be reduced. By knowledge of the causes of this reduction and by use of methods for increasing cardiac output, we can now nearly always avoid serious reductions in cardiac output. This early after operation ventricular end-diastolic pressure, or so-called ventricular filling pressure, is elevated by augmentation of blood volume with whole blood or crystalloid solutions, depending upon the situation. Left and right atrial pressures are continuously monitored in order that the augmentation of blood volume does not exceed safe limits. When myocardial contractility is depressed, digitalis is administered. If myocardial depression is acute, isoproterenol or epinephrine is administered by continuous infusion. In patients with tetralogy of Fallot who show a depression of cardiac output early after intracardiac operation, the heart begins to recover within about 48 hours when the patient is properly managed. Soon thereafter cardiac output becomes normal and convalescence proceeds uneventfully.

Similar detailed knowledge now exists concerning pulmonary and renal performance early after these operations. The amounts and distribution of water and solutes in the body undergo changes early postoperatively that are at times profound. We are at present involved particularly in investigations of these, using radioisotopic techniques.

HOSPITAL MORTALITY AND MORBIDITY

Permanent heart block has occurred rarely in our experience in the past 5 years. This, plus better understanding of the operative and postoperative details necessary for survival have resulted in the operative mortality being generally less than 10 per cent in recent years (Fig. 20). During this time about three-fourths of our patients have had the severe form of the disease and many have had one or more previous operations. It is interesting to compare the results in the first 50 cases

Table I

TETRALOGY OF FALLOT*
INTRACARDIAC REPAIR

	First 50 Patients†		Last 50 Patients‡	
	Total	Hospital Deaths	Total	Hospital Deaths
Mild Form	—	—	3	
Moderate Form	21	3	11	1
Severe Form	26	11	17	1
Previous Blalock Operation	3	2	10	
Previous Potts' Operation	—	—	5	
2 Previous Operations	—	—	4	
Total	50	16 (32%)	50	2 (4%)

* Hospital mortality rates after open operation for the tetralogy of Fallot, in the first 50 patients and in the last 50 patients. All of the early cases were operated upon at the Mayo Clinic. About two-thirds of the recent cases were operated upon at the University of Alabama Medical Center.
† April, 1955 to August 15, 1967.
‡ March, 1966 to September 1, 1967.

(operated upon between April, 1955 and August 15, 1967) and in the last 50 (operated upon between March, 1966 and September, 1967). The hospital mortality rate was 32 per cent in the first 50, and 4 per cent in the last 50 (Table 1). One of the deaths in the last 50 cases was from infection and one from pulmonary edema which was probably the result of overtransfusion. Both deaths were preventable.

Obviously, there is now sufficient knowledge that, when it is applied with skill, a very low operative mortality results. This is attested to by the experience of a number of surgeons. Actually, if we could ever reach a point where no human error occurred, the mortality with present knowledge would be 1 to 2 per cent.

LATE RESULTS

Most patients have an excellent result from the operation. Specifically, knowledge of the late results is available in 232 patients operated upon by my colleagues and the author. Ninety-three per cent are fully active and without symptoms, and their life expectancy should be normal. Four per cent have a good result, but have mild limitation of exercise tolerance. Only 3 per cent have a late result that is for some reason unsatisfactory. Such results are truly remarkable when one considers the pitiful state of most of the patients preoperatively.

CONCLUSION

An experience of 12 years, encompassing operations in 603 patients with tetralogy of Fallot between April 1, 1955 and September 1, 1967, has been used as the basis for this presentation. New knowledge has been developed, in part from this experience, but also from the contributions of numerous surgeons, pediatric cardiologists, radiologists, cardiologists, pathologists, physiologists, and anesthesiologists. Those wishing to apply this knowledge skillfully must study, practice pitiless self-criticism, and continuously seek advice from colleagues and students.

Today literally thousands of patients

live and enjoy good health as a result of the knowledge and skill of many surgeons throughout the world. The accumulated experience is being taught to younger colleagues in the cardiovascular teaching centers of the world. The new knowledge which has also resulted from this experience affects not only cardiovascular surgery, but illuminates some hitherto dark areas of physiology, cardiology, radiology, medicine, and general surgery. In all of these facets lies the importance of the development of open intracardiac surgery for the tetralogy of Fallot.

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RADIOISOTOPE SCANNING OF THE LUNGS IN PATIENTS WITH SYSTEMIC-PULMONARY ANASTOMOSES*

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LUNG scanning by means of intravenously injected radioactive particles has proven to be a safe, simple and reliable method of measuring regional pulmonary arterial blood flow in pulmonary embolism, pulmonary emphysema, pulmonary tuberculosis, bronchogenic carcinoma, asthma and mitral valve disease.[3,6,7,8,11,12] The reduction of regional pulmonary arterial blood flow due to pulmonary stenosis is the main cause of symptoms and signs in cyanotic congenital cardiac disease. Increasing regional pulmonary arterial blood flow by means of anastomosing a large systemic artery to the pulmonary circulation has benefited this group of diseases by increasing pulmonary blood flow.[1] Although complete correction of the cardiac malformations of tetralogy of Fallot is preferred, there is still a place for the use of the technically simpler procedure of systemic to pulmonary anastomosis for palliation in situations in which complete correction is not feasible.[10] When the condition of the patient deteriorates following such a shunt procedure, it is important to know whether or not the anastomosis is functioning properly. The purpose of this communication is to evaluate the usefulness of lung scanning in determining the functional condition of the surgical shunt in this situation.

MATERIAL AND METHODS

The lung scans and clinical records of 8 patients who had lung scanning performed following systemic to pulmonary anastomosis since January, 1967 were reviewed. One patient had a scan prior to surgery. Scanning was performed from the posterior aspect following an intravenous injection, with the patient supine, of 2.3 μc per kg. of I^{131} macroaggregated albumin (MAA).* A commercially available Picker Magnascanner was used. The time constant was modified to 1/32 of a second and the light pipe was changed to a 5×2 mm. rectangle with a coping saw. No contrast enhancement other than film recording was necessary because of a high-target to non-target ratio of radioactivity; therefore, the contrast range used was 100 per cent of full scale (100 counts per minute differential). Scanning speed was varied according to maximum count rate.

Six of the 8 patients had right and left sided cardiac catheterization performed along with cineangiocardiography.

Seven patients had a Blalock-Taussig procedure performed, with an end-to-side anastomosis between the subclavian artery and one main pulmonary artery in 6 patients, and an end-to-end anastomosis in one. One of these patients had a previous Potts procedure which had become nonfunctional. One patient had a Cooley procedure with anastomosis of the ascending aorta to the right pulmonary artery.

RESULTS

Correlation of pertinent clinical, catheterization and scanning data are presented in Table I. The features of the preoperative appearance of the lung scan found in 2 patients (one not operated upon and hence not included in the series) are shown in Figure 1*A*. Evidence of shunting of blood from the right side of the circulation to the left side was present in both with activity

* Obtained from Mallinckrodt Nuclear, St. Louis, Missouri.

* From the Department of Radiology, Section of Radioisotopes, Indiana University Medical Center, Indianapolis, Indiana.
† Assistant Professor of Radiology.
‡ Resident in Radiology.

Table I

CLINICAL, CATHETERIZATION AND SCANNING DATA

Case	Diagnosis	Age	Arterial O_2—Per Cent Saturation	Right Ventricle Pressure (mm. Hg)	Left Ventricle Pressure (mm. Hg)	Surgery	Postoperative Lung Scan	Evaluation of Shunt
I	Tetralogy of Fallot	4 yr	82	106/14	104/19	March 13, 1967: End-to-side right subclavian to right pulmonary artery	March 16, 1967: Equal perfusion of right and left lung	Shunt murmur present; improved exercise tolerance
II	Tetralogy of Fallot	4 yr.	76	127/11	107/13	March 27, 1967: End-to-side right subclavian to right pulmonary artery	March 30, 1967: Right lung has decreased perfusion	Shunt murmur present
III	Tetralogy of Fallot	3 yr.	83	99/8	122/11	January 24, 1967: End-to-side right subclavian to right pulmonary artery	January 27, 1967: Right lung has markedly decreased perfusion	Shunt murmur variable; patent on cineangiography
IV	Tricuspid atresia	2 yr.	67		83/6	January 18, 1967: End-to-side left subclavian to left pulmonary artery	February 25, 1967: Right lung has markedly decreased perfusion	Shunt murmur variable; patent on cineangiography; no filling of right pulmonary artery
V	Tetralogy of Fallot	6 yr.	86	74/9	115/18	March 2, 1967: End-to-side left subclavian to left pulmonary artery	March 9, 1967: Equal perfusion of right and left lung; splinting left lung	Shunt murmur present
VI	Endocardial cushion defect Pulmonary banding	5 yr.	76	86/5	93/10	April 26, 1967: Ascending aorta to right pulmonary artery	May 4, 1967: Left lung has diminished perfusion	Loud shunt murmur present
VII	Tetralogy of Fallot	17 yr.				January 8, 1955: Left subclavian to left pulmonary artery	May 2, 1967: Right lung is less well perfused than the left	Shunt murmur present; good exercise tolerance
VIII	Tetralogy of Fallot	17 yr.				August 7, 1954: End-to-end left subclavian to distal left pulmonary artery	January 30, 1967: Right lung markedly diminished perfusion; left lung diminished perfusion with focal defect	After 12 years shunt murmur disappeared and patient deteriorated; shunt clinically closed at the time of scanning

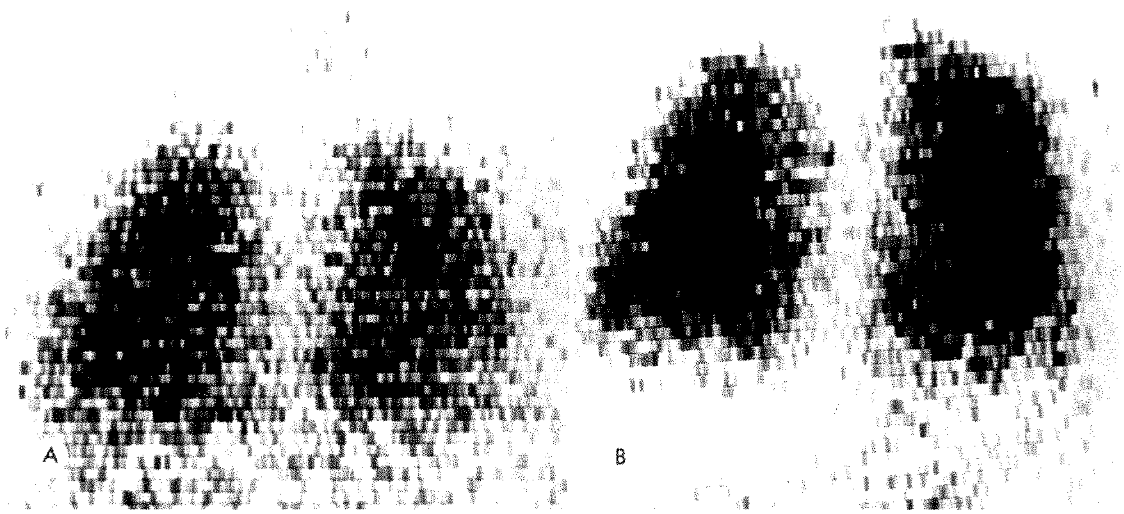

Fig. 1. Case I. (*A*) Preoperative scan in patient with tetralogy of Fallot shows equal perfusion of both lungs. The somewhat uneven appearance of the scan is due to statistical variation because of the low count rate and a scanning speed too fast for the count rate. Activity in the thyroid and the kidneys indicates right-to-left intracardiac shunting of particles by way of a large high intraventricular septal defect shown on cineangiocardiography. (*B*) Following anastomosis of the right subclavian artery to the right main pulmonary artery, perfusion to the lungs appears equal.

in the thyroid and renal areas. Regional pulmonary arterial blood flow appeared approximately equal in one lung as compared to the other in 1 patient, and slightly unequal in the other. Following a surgical shunt, the lung scan in 1 of the 8 patients appeared normal (Fig. 1*B*), and in 5 it showed unequal activity of one lung as compared to the other (Fig. 2). The lung with apparently decreased perfusion was on the side of the systemic to pulmonary anastomosis in 2 patients and on the side opposite the anastomosis in 4 patients. In all but 1 patient there was good clinical evidence, including the presence of a continuous murmur and increased exercise tolerance, that the shunt was patent at the time the lung scan was performed. In 2 patients, both scanning and cineangiography were performed following surgery. In one of these patients, the scan showed decreased activity on the side of the anastomosis (Fig. 3*A*), while the cineangiographic study showed the anastomosis to be functioning (Fig. 3, *B–D*). In the other patient, the scan showed no activity in the right lung, the side opposite the anastomosis (Fig. 4*A*). The patient improved clinically and a repeat scan 2 weeks later showed perfusion of the upper portion of the right lung (Fig. 4*B*). Cineangiography after the second scan showed no filling of the right main pulmonary artery, which was thought to be occluded (Fig. 4, *C* and *D*).

Fig. 3. Case III. (*A*) Lung scan following a right Blalock-Taussig procedure in a patient with tetralogy of Fallot shows reduction of activity in the right lung suggesting reduced perfusion via the pulmonary artery because of streaming or dilutional effect from the surgical anastomosis. There is a moderate amount of activity in the kidneys but the amount of intracardiac right-to-left shunting cannot be estimated because particles coming through the aorta may be diverted through the surgical anastomosis.

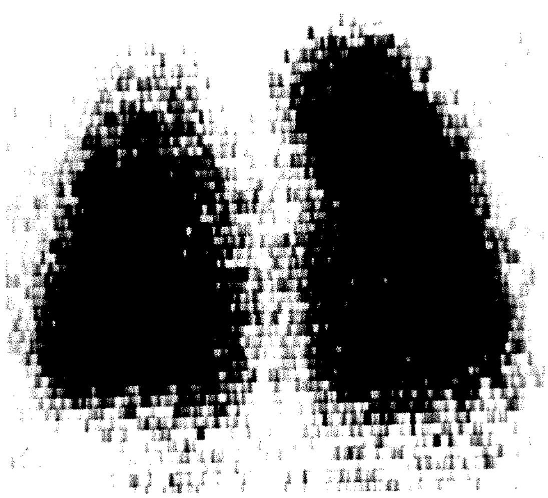

Fig. 2. Case II. The lung scan following a Blalock-Taussig shunt procedure on the right shows diminished activity in the right lung compared to the left. This does not mean that there is less total blood flow to the right lung, but probably represents a dilutional effect on the blood coming through the pulmonary artery by blood flow through the surgical shunt that does not carry much activity because there is only a small amount of intracardiac shunting.

DISCUSSION

There are two factors which complicate evaluation of regional pulmonary arterial blood flow by means of the scanning technique in patients who have communications between the pulmonary and systemic circulations at two levels. In patients with significant intracardiac venous to arterial shunting of blood, particles will be carried into the cerebral circulation and the possibility of sequelae from multiple small

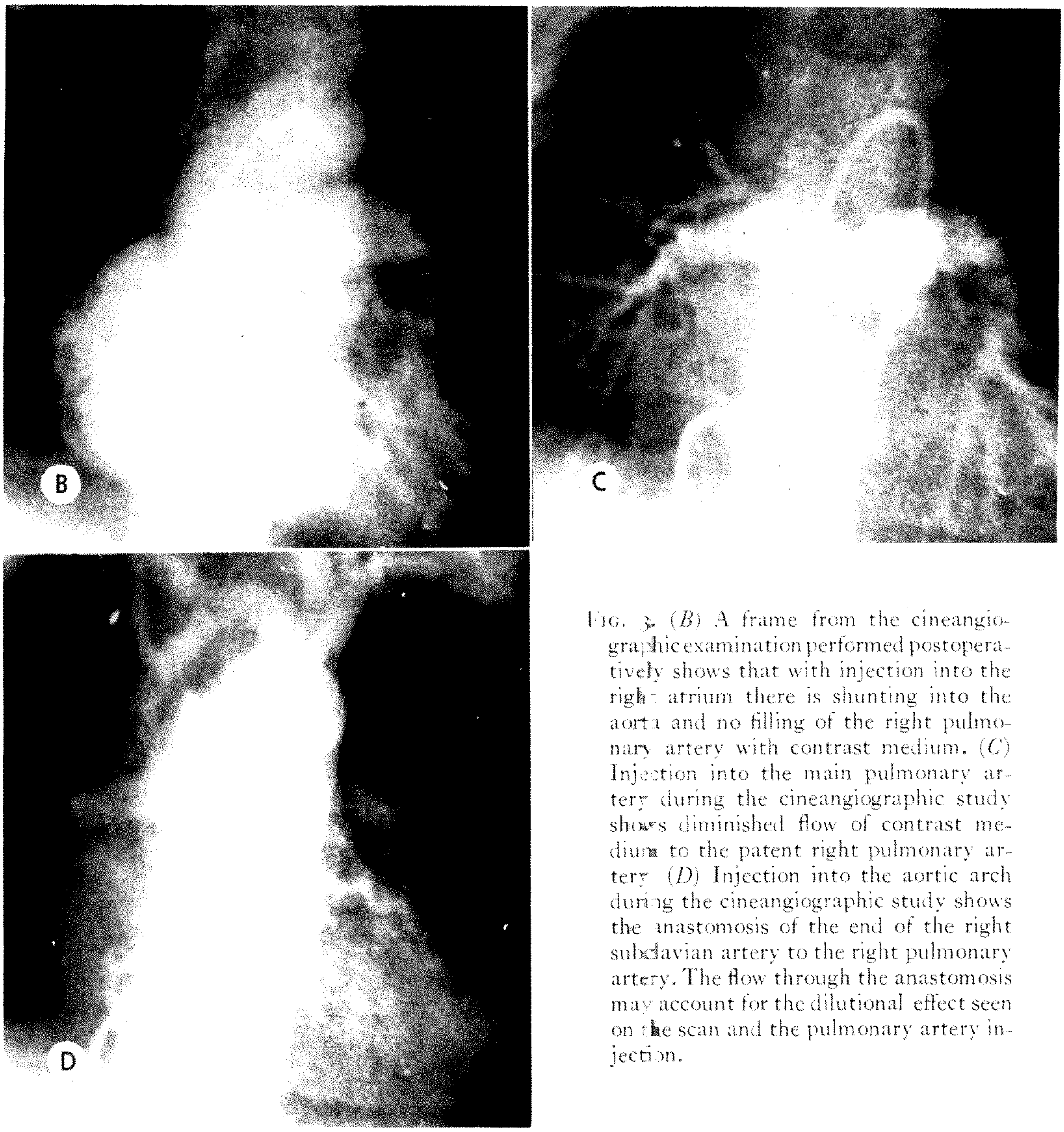

FIG. 3. (*B*) A frame from the cineangiographic examination performed postoperatively shows that with injection into the right atrium there is shunting into the aorta and no filling of the right pulmonary artery with contrast medium. (*C*) Injection into the main pulmonary artery during the cineangiographic study shows diminished flow of contrast medium to the patent right pulmonary artery. (*D*) Injection into the aortic arch during the cineangiographic study shows the anastomosis of the end of the right subclavian artery to the right pulmonary artery. The flow through the anastomosis may account for the dilutional effect seen on the scan and the pulmonary artery injection.

emboli in the arterioles and capillaries of the brain must be considered. Experiments with direct intracarotid injection of radioactive particles in primates and in man have shown this procedure to usually be safe;[4,9] however, one group of investigators reported sequelae in 3 of 12 patients who had particles injected in the carotid arteries.[5] With the use of high specific activity particles under 50 μ in diameter this possibility becomes more remote. At this institution 12 patients with known pulmonic to systemic intracardiac shunts have had no difficulty after lung scanning and there is no report of such an occurrence with routine lung scanning.

The other difficulty lies in interpreting the scan pattern in terms of blood flow to the lungs when there is a systemic to pulmonary shunt at the level of one main pulmonary artery. Experimental work in dogs with surgically made systemic to pulmonary shunts has shown that if radioactive particles are injected intravenously, most of the particles will go to the pulmonary arteriolar-capillary bed on the side oppo-

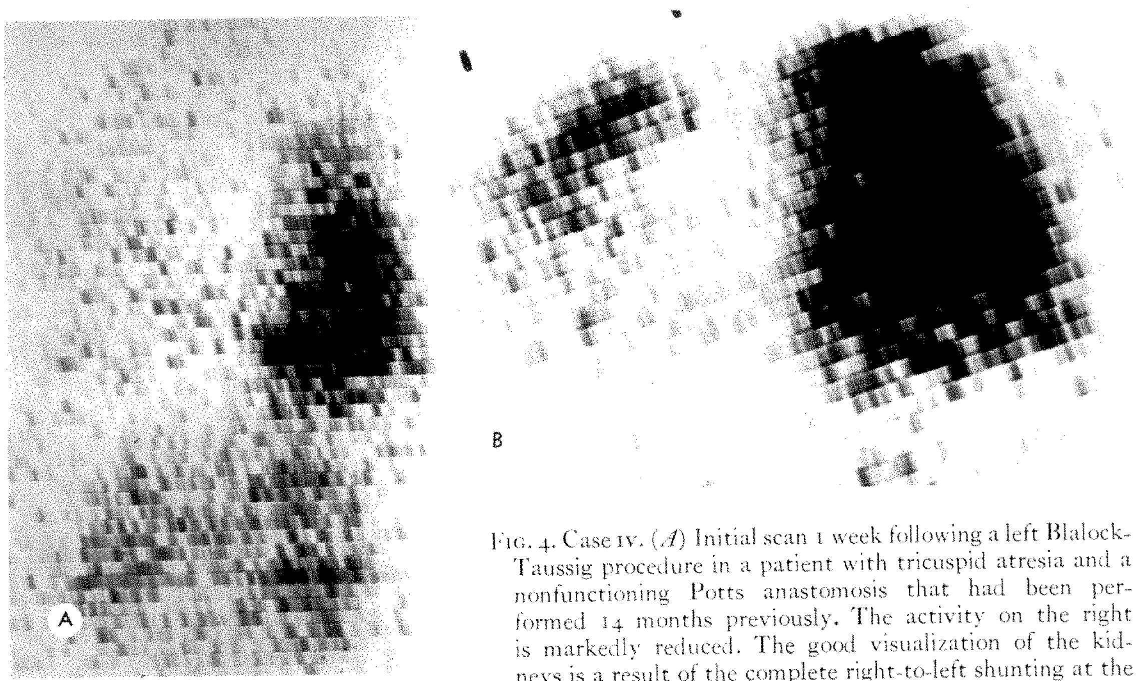

Fig. 4. Case iv. (*A*) Initial scan 1 week following a left Blalock-Taussig procedure in a patient with tricuspid atresia and a nonfunctioning Potts anastomosis that had been performed 14 months previously. The activity on the right is markedly reduced. The good visualization of the kidneys is a result of the complete right-to-left shunting at the atrial level. (*B*) A repeat lung scan 13 days later shows improvement of perfusion to the right upper lung perhaps resulting from development of systemic collateral circulation to the lung. The activity in the left lung comes almost entirely from the Blalock-Taussig anastomosis. The patient had improved clinically since the first scan.

site the shunt, while if an intra-aortic injection of particles is made, most of the particles will be lodged in the pulmonary arteriolar-capillary bed on the side of the shunt.[2] The situation is complicated when intracardiac shunting of blood exists and

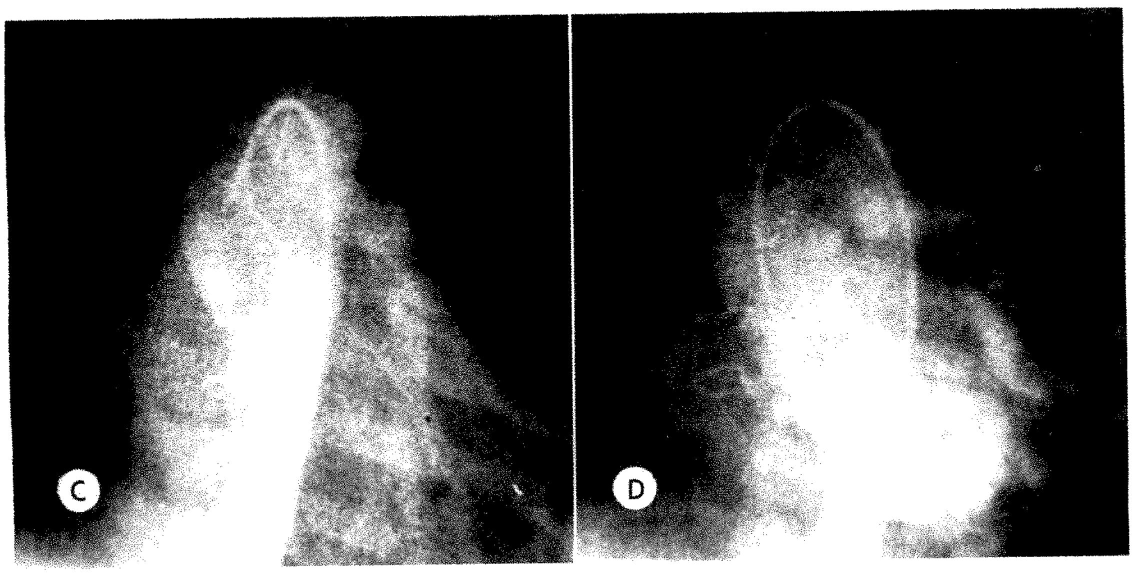

Fig. 4. (*C*) A frame from the postoperative cineangiographic study shows injection of contrast medium into the aortic arch. The functioning left Blalock-Taussig anastomosis directs the contrast medium into the left pulmonary artery. The right pulmonary artery did not opacify with contrast medium. (*D*) Injection into the left ventricle filled a small anterior right ventricle. The right pulmonary artery did not opacify with contrast medium. It is thought to be occluded.

one cannot be certain how many of the particles reach the pulmonary circulation via the right ventricle and main pulmonary artery, and how many particles reach the pulmonary circulation by means of the intracardiac shunt via the aorta and the systemic to pulmonary anastomosis. Prior to surgery, the amount of activity in the kidneys should provide a qualitative estimate of intracardiac shunting of blood.

Following a surgical anastomosis, particles that are shunted from right to left in the heart could flow in greater quantity through the subclavian artery used for anastomosis because it is now part of the low resistance pulmonary circulation. This means fewer particles will reach the kidneys and therefore the amount of activity in the kidneys in the postoperative scan cannot indicate the amount of right-to-left intracardiac shunting of blood. Without knowledge of the quantity of right-to-left intracardiac shunting, we could not estimate whether most of the particles reached the pulmonary arteriolar-capillary bed by way of the right side of the heart and main pulmonary artery or by way of right-to-left intracardiac shunting, through the aorta and surgically created systemic to pulmonary anastomosis. If most of the particles are carried through the pulmonary artery, then one might expect less of the particles to lodge in the pulmonary arteriolar-capillary system on the side of the systemic to pulmonary anastomosis, since the blood flow on this side would be diluted by systemic blood flow. In this case a diminished amount of activity in the lung on the side of the shunt would indicate that the shunt was patent (Fig. 3*A*). On the other hand, if most of the blood flow reaching the pulmonary arteriolar-capillary bed came through the aorta and surgical systemic to pulmonary shunt via an intracardiac shunt, then most of the particles would be found on the side of the surgical shunt if it were open (Fig. 4, *A* and *B*). Alternatively, the effects of shunting at two levels, the intracardiac and the surgical systemic to pulmonary anastomosis, may balance one another and the scan activity would appear relatively equal (Fig. 1*B*). Since one cannot know the degree of intracardiac shunting of blood, one cannot interpret the unequal distribution of activity in the lungs to mean that the shunt is patent or obstructed.

SUMMARY

Clinical, catheterization and lung scanning data of 8 patients who had surgical systemic to pulmonary shunts performed to increase pulmonary arterial blood flow were correlated in an attempt to evaluate the reliability of the lung scan in predicting whether or not the shunt was patent.

Two unknown variables control the distribution of radioactive particles to the lungs, the degree of intracardiac shunting and the amount of blood carried to the pulmonary circulation via the surgical shunt. The predominance of one or the other of these factors will cause unequal distribution of the particles to the pulmonary arteriolar-capillary bed and consequently an asymmetric appearance on the lung scan, even in the presence of a functioning shunt. Under more balanced conditions, a symmetric appearance will be seen on the lung scan.

Thus the lung scan cannot be readily interpreted to mean that the surgical shunt is functioning or nonfunctioning.

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CREATION OF ATRIAL SEPTAL DEFECTS BY CATHETER AS PALLIATION OF COMPLETE TRANSPOSITION*

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IN OVER 80 per cent of patients with complete transposition of the great vessels, congestive cardiac failure and death occur in early infancy. The outlook for these critically ill infants has, however, considerably improved because of newer operative techniques. Although total operative correction of complete transposition of the great vessels is feasible in infancy the mortality associated with this procedure early in life is prohibitive, especially among the seriously ill infants who form the majority of patients with this condition. As an alternative, operative creation of an atrial septal defect has proven to be useful palliative procedure, but is also associated with a significant operative mortality. Recently a technique to create an atrial septal defect by a cardiac catheter has been described.[8] This procedure has a low mortality since it eliminates the need of general anesthesia and thoracotomy.

In this paper, the previous methods of creating atrial septal defects are briefly reviewed. Two new techniques which have been used to create atrial septal defects in animals are also described. In addition, the results of our experience using a balloon-Rashkind catheter technique in 6 severely ill infants with cyanotic congenital heart disease are presented.

REVIEW OF PREVIOUS TECHNIQUES

In 1926, Dmitrieff[4] first experimentally created an atrial septal defect by a technique of digitally invaginating the atrial appendages to identify the atrial septum and then thrusting a small clamp through the septum and enlarging the defect with a finger placed through the opposite appendage. Cohn[3] in 1947 created an atrial septal defect by inserting a hemostat through the left atrial appendage and opening it in the septum. Martin and Essex,[7] and Swan *et al.*[9] advanced a scalpel through the atrial appendage to the vicinity of the septum and incised it blindly. Blalock and Hanlon[1] in 1948 published their classical procedure for creating a septal defect by partial excision of the atrial septum. Margutti *et al.*[6] used a special guide wire punch device. Boerema *et al.*[2] utilized hypothermia and created atrial defects under direct vision. Friend and co-workers[5] in 1965 described a new technique developed in dogs for producing atrial septal defects with the use of a corneal trephine under the conditions of temporary venous inflow occlusion. A variety of other instruments and techniques have been used by various investigators, and are reviewed by Friend *et al.*[5]

In 1966 Rashkind and Miller[8] described a technique for producing atrial septal defects without thoracotomy or general anesthesia. A balloon tipped catheter (No. 6½ French) was used. The catheter was passed by way of the femoral vein into the right atrium and then through the foramen ovale to the left atrium. The balloon was inflated with 2–6 cc. of radiopaque solution and was withdrawn into the right atrium tearing the atrial septum. This was repeated until the balloon could be withdrawn without resistance from the left to the right atrium.

OBSERVATIONS

EXPERIMENTAL STUDIES

Atrial septal defects were created experimentally in dogs by either electrocautery or a mechanical device. Under Surital anes-

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thesia, the right femoral vein was exposed and a Brockenbrough needle with a No. 8 teflon catheter was advanced under fluoroscopic control into the left atrium. The puncture needle was removed and a stainless steel basket was advanced through the catheter into the left atrium (Fig. 1). The basket was opened to 1.5 cm. in diameter and connected to a powerful electrocautery. By pulling gently on the basket and closing the current, a fair sized hole in the atrial septum could be produced. The small amount of gas produced due to the action of the cautery did not seem to cause noticeable gas embolism and electrical deaths were not observed. The atrial septal defect thus produced was, however, characterized by irregular, shaggy borders (Fig. 2). The atrial septal defect was patent after one month in only one animal. There was, in addition, a 50 per cent mortality due to hemopericardium. Because of these results, the procedure was not thought to be suitable for human use.

Since the anatomy of the canine atrial septum is quite different from that of humans, additional experimental studies were performed on human cadavers using various mechanical devices. The most promising instrument was a stainless steel bow with a Gigli saw wire (Fig. 3) which produced cuts of considerable length in the fossa ovalis. This seemed to be a safer cutting device since only structures under tension such as the atrial septum could be incised in these cadavers. To date, this technique has not been used in humans.

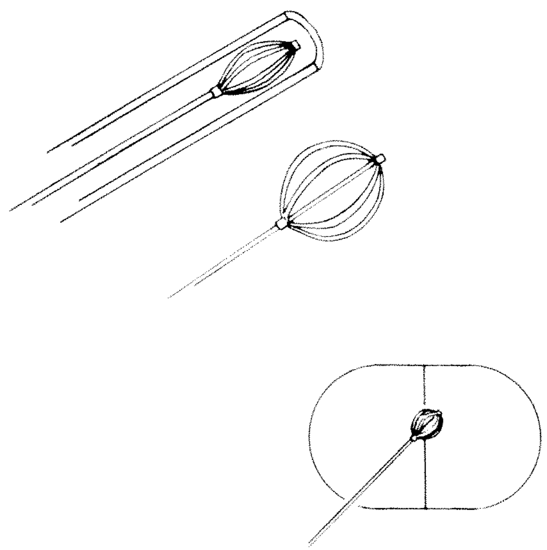

Fig. 1. Wire basket. *Top:* Introduced through catheter. *Middle:* Expanded. *Bottom:* Pulling through fossa ovalis.

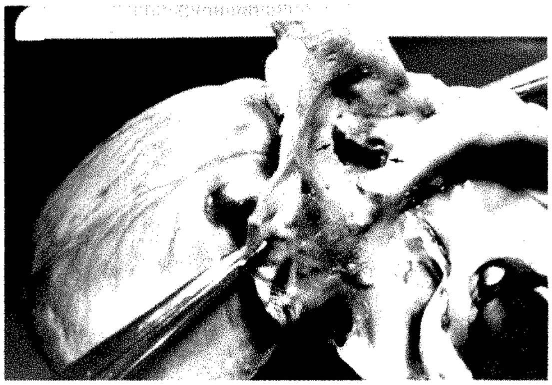

Fig. 2. Atrial septal defect in dog heart created by cautery technique.

RESULTS OF BALLOON CATHETER TECHNIQUE IN INFANTS

In 6 severely ill infants the creation of an atrial septal defect has been attempted using the balloon catheter technique. Among the 6 infants, complete transposition of the great vessels was present in 5,

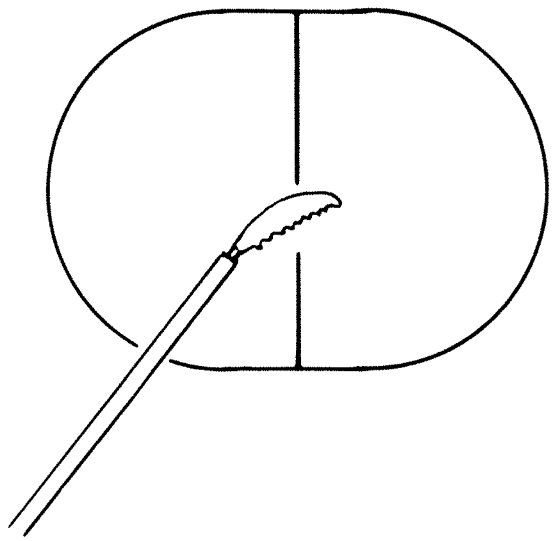

Fig. 3. Stainless steel bow with Gigli saw.

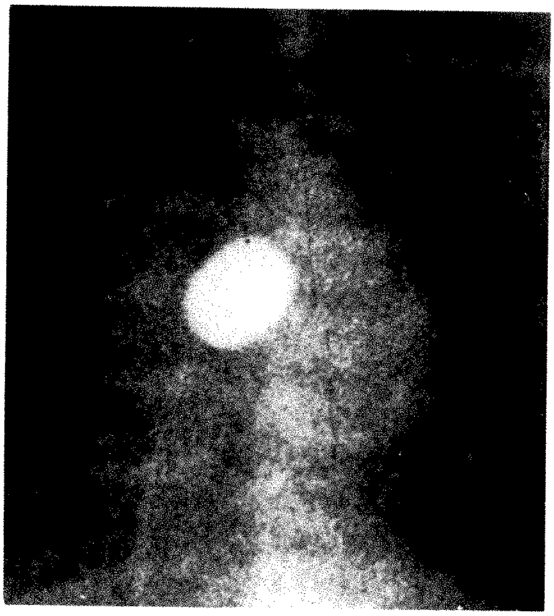

FIG. 4. Cineradiographic frame during balloon dilatation of foramen ovale. Note position of balloon in left atrium.

and mitral atresia in 1. The cases illustrate the variability of success of this procedure.

REPORT OF CASES

CASE I. *Transposition of Great Vessels.* A 7 day old, markedly cyanotic patient with complete transposition of the great vessels and pulmonary stenosis was admitted to the University of Minnesota Hospitals and underwent immediate balloon catheter dilatation of the foramen ovale. Under local anesthesia, the saphenous vein was exposed and a No. 6 Fogarty catheter was introduced and advanced without difficulty across the foramen ovale into the left atrium. Due to the moribund condition of the patient, no blood samples were obtained. The balloon was inflated with contrast material and under fluoroscopic control was pulled through the foramen ovale several times with success with increases in the amount of inflation (Fig. 4). The patient tolerated the procedure well and several observers felt that his color had improved. A venous angiogram was performed which showed more pronounced opacification of the left atrium following the catheterization (Fig. 5, *A* and *B*). At the age of 37 days, the patient returned for a repeat angiogram because of increasing cyanosis and cardiac failure. At this time, no significant shunt was demonstrable and the balloon dilatation of the fossa ovalis was repeated. Blood oxygen samples were taken prior and after the dilatation. No significant change in oxygenation was demonstrable, and repeat angiogram did not demonstrate improved opacification of the left atrium. Because of further deterioration of the patient's condition, a Blalock-Hanlon operation was performed at the age of 41 days.

CASE II. *Mitral Atresia.* The second patient was a 3 month old cyanotic baby in whom presence of mitral atresia with obstruction at the foramen ovale was documented by cardiac catheterization and angiography. Because of pulmonary venous obstruction due to a small foramen ovale, enlargement of the atrial septal defect with a balloon catheter was thought to be desirable. Under local anesthesia a No. 5 Fogarty catheter was passed into the left atrium and pulled through the atrial septal defect with great difficulty. In spite of rather extreme force which seemed to pull the heart toward the diaphragm, the high resistance at the foramen ovale could not be overcome. The patient came to postmortem examination a few days later and a careful analysis of the atrial septal defect failed to disclose any recent tear (Fig. 6) and an unusually thick septum.

CASE III. *Transposition of Great Vessels.* This 10 month old infant was first seen at the University of Minnesota Hospitals at 10 days of age because of cyanosis and respiratory distress since birth. On admission he exhibited marked cyanosis and the findings of congestive cardiac failure. Some initial improvement recurred in response to digitalization. Venous angiography done 3 days after admission revealed transposition of the great vessels.

The infant was returned to the catheterization laboratory and attempts were unsuccessful to pass a balloon catheter into the left atrium. Three days later a Blalock-Hanlon procedure with banding of the pulmonary artery was carried out and the child had an uneventful postoperative period. He has shown improvement with modest weight gain. There is still evidence of moderate cyanosis but no cardiac failure.

CASE IV. *Transposition of Great Vessels.* This 6 month old infant was admitted to the University of Minnesota Hospitals at 3 weeks of age with a history of progressive cyanosis since birth. The child revealed the findings of

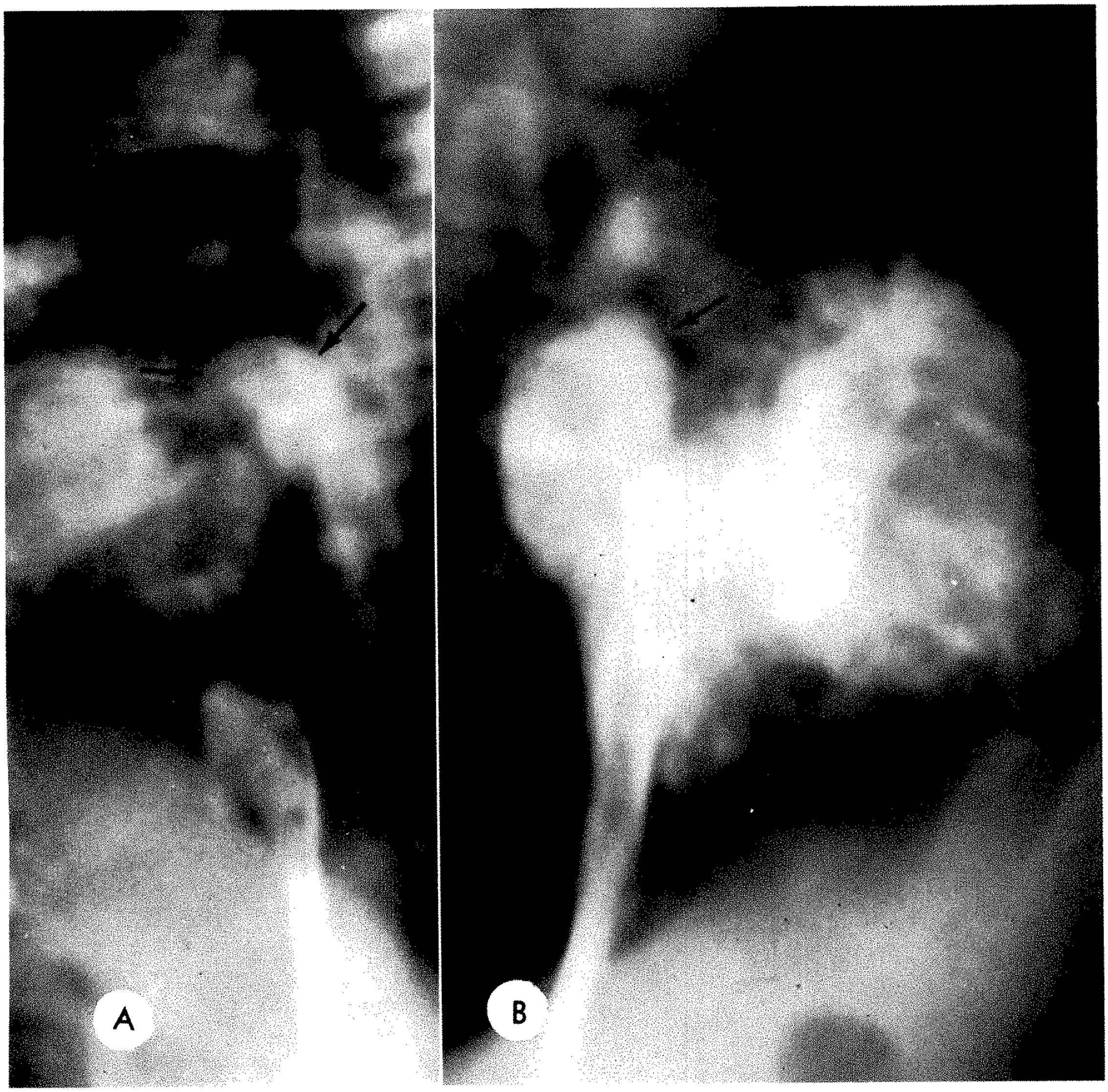

FIG. 5. (*A*) Forward angiogram showing mild opacification of the left atrium and transposed aorta. (*B*) Forward angiogram following balloon dilatation. Note the denser opacification of the left atrium.

congestive cardiac failure and received appropriate treatment. On the day following admission, venous angiocardiography was carried out and revealed complete transposition of the great vessels with intact ventricular septum.

Surgical consultation was obtained and while awaiting a Blalock-Hanlon procedure, the child became critically ill and was in shock.

Balloon catheterization was carried out as an emergency procedure and considerable improvement in the condition of the child occurred immediately following the procedure. The degree of cyanosis was less and respirations were less labored. The child showed a steady weight gain and was discharged at 5 weeks of age. Subsequently the child was re-examined at 5 months of age and has shown a 4 pound weight gain since birth. Mild to moderate cyanosis was present. There was no respiratory distress or evidence of cardiac failure.

CASE V. *Transposition of Great Vessels.* This 2 month old infant developed cyanosis and respiratory distress at 1 week of age. She was admitted at 3 weeks of age with moderate cyanosis and severe congestive cardiac failure. A good response occurred following administration of Lanoxin. Cardiac catheterization and

FIG. 6. Postmortem specimen with guide passed through foramen ovale in patient with mitral atresia. No recent tear of fairly thick fossa ovalis.

selective angiography revealed complete transposition of the great vessels with intact ventricular septum.

A No. 5 Fogarty catheter was advanced into the left atrium and the balloon inflated. The catheter was withdrawn across the atrial septum. This was repeated several times, with progressively less resistance to withdrawal. Despite the apparent ease with which the balloon procedure was done, the infant showed little clinical improvement, so that a Blalock-Hanlon procedure was carried out 3 days later.

CASE VI. *Transposition of Great Vessels.* This $3\frac{1}{2}$ week old male infant was admitted to the University of Minnesota Hospitals with a history of cyanosis and cardiomegaly since birth. On admission evidence of cardiac failure was present. Following digitalization, cardiac catheterization and selective angiocardiography revealed complete transposition of the great vessels with intact ventricular septum. At the time of catheterization a No. 5 Fogarty catheter was advanced to the left atrium and inflated. The inflated balloon was withdrawn three times across the atrial septum; each time decreasing resistance was met. Following the procedure, the infant was less cyanotic, and exhibited less respiratory distress. His status, however, was not sufficiently improved, so that a Blalock-Hanlon procedure was done 1 week later.

COMMENTS

The creation of atrial septal defect by a technique under local anesthesia is very desirable since general anesthesia alone may have a high mortality rate in critically ill patients with transposition of the great vessels. In spite of the fact that our series is too small to draw any final conclusions, it is likely that the success of this procedure depends largely on the anatomy in the region of the fossa ovalis. In the second patient with mitral atresia, the fossa ovalis was relatively thick preventing successful tear. This experience was also evidenced by numerous balloon dilatations performed on cadavers of newborns and infants. Beyond the age of 3 months, it seemed to be impossible to cause a tear in the fossa ovalis due to the rather firm fibrous edge of the foramen. It is hoped that one of our mechanical devices, perhaps in combination with a balloon may yield better results, although it is doubtful that excellent mixing produced by surgical excision of the atrial septum can be paralleled by any of the closed procedures. Until a reliable closed technique can be devised, surgery remains the procedure of choice except in very ill infants.

Our experience in attempting to create interatrial communications in 6 infants, illustrates the frustrations and successes of this technique. In 2 cases, 1 with mitral atresia and the other with transposition of the great vessels, we were unable to advance the catheter tip into the left atrium. In 3 other cases the procedure could be carried out, and a fully inflated balloon withdrawn easily across the atrial septum. Such cases exhibited some improvement, but subsequently required a Blalock-Hanlon procedure. Perhaps in these cases, no enlargement of the foramen ovale was created, but merely the balloon was passing between the two leaflets of the foramen ovale, or the foramen was perhaps only stretched. Finally, in 1 case, clinical im-

provement following the procedure was sufficiently great, that the child could be discharged. Five months later she is doing relatively well.

Despite these over-all discouraging results, this procedure is a useful, and occasionally beneficial therapeutic adjunct, which can be performed in conjunction with diagnostic cardiac catheterization without adding significantly to the duration of the catheterization. It may be life-saving in the critically ill child as in our Case IV, and may provide sufficient improvement, so that the child is in improved cardiopulmonary status for operative intervention. It must be remembered that not all cases of transposition of the great vessels will be benefitted by this technique. Prior angiocardiography is therefore required in order to delineate the defects. Certainly patients with transposition of the great vessels and intact ventricular septum are the prime candidates for creation of an atrial communication which permits mixing of the systemic and pulmonary venous returns. On the other hand, those patients with transposition and a ventricular septal defect have a means of mixing, but are generally in difficulty because of excessive pulmonary blood flow. In these patients little benefit can be expected from creation of an atrial communication, but rather pulmonary artery banding is the procedure of choice.

SUMMARY

The experimental methods of creating atrial septal defects are briefly reviewed. Our own experimental approach and results in dogs are described.

Six patients underwent the closed balloon catheter dilatation of the foramen ovale as described by Rashkind and Miller[8] and the results obtained warrant the use of this technique as an emergency procedure.

One patient is of particular interest since postmortem evaluation of the procedure was possible.*

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* We have performed balloon catheterizations in 3 additional infants with complete transposition of the great vessels. In one infant significant clinical improvement occurred so that he was discharged and is being followed on an outpatient basis. A second infant subsequently required a Blalock-Hanlon operation, while the third infant suddenly expired 36 hours following the catheterization procedure.

CORRELATION OF ROENTGEN FINDINGS WITH HEMODYNAMIC DATA IN PURE MITRAL STENOSIS*

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IN THE evaluation of patients with mitral stenosis, it is essential to separate those individuals with mild forms of the disease from those requiring surgical intervention. The present study was undertaken to define the roentgen signs that are useful in separating these 2 groups of patients.

There are many reports in the literature relating the roentgen signs of mitral stenosis to the hemodynamic data.[1,2,4,6,17,18,21,25,27] However, not all authors have found the various signs of equal diagnostic use. For example, Milne,[17] Moore *et al.*[18] and Jacobson *et al.*[9] demonstrated good correlation between the mean pulmonary artery pressure (MPAP) and the size of the pulmonary artery segment on the frontal roentgenogram of the chest. On the other hand, Melhem *et al.*[16] and Simon[24] could not demonstrate significant correlation between the mean left atrial pressure and the size of the left atrium. Simon questioned the reliability of the roentgenography and criticized the use of esophagography in the evaluation of patients with mitral stenosis. Kerley's B lines and abnormal pulmonary vascular patterns have proved useful in assessing pulmonary pressures and resistances.[2,4,6,9,16,17,27] In this study a variety of roentgen signs were related to physiologic data acquired in the catheterization laboratory, to the calculated size of the mitral valve orifice and to the findings at surgical exploration.

MATERIAL AND METHODS

Sixty patients seen in the Cardiovascular Laboratory between March 22, 1960 and June 8, 1966 were selected for analysis. There were 47 females and 13 males. The patients ranged in age from 15 to 62 years (mean 40.5 years). Eleven of the 60 patients had undergone previous mitral valvotomy but were included in the present study because of the development of re-stenosis.

All patients had pure mitral stenosis as determined by complete right and left heart catheterization[15] including transseptal catheterization of the left atrium. Cardiac output was estimated by both the dye dilution technique and by the Fick principle.

The roentgenographic examination ranged from a single posteroanterior view of the chest to a 4 view cardiac series with barium in the esophagus. The roentgenograms reviewed for this study were obtained within 30 days of the cardiac catheterization.

ROENTGENOGRAPHIC SIGNS

(Table I)

1. KERLEY'S B LINES

These were defined as fine parallel linear densities in the peripheral lung fields, perpendicular to a pleural surface and usually seen in the costophrenic sulci. Distinct Kerley's lines referred to sharp lines 2 or more cm. in length extending peripherally to the pleural surface. Indistinct Kerley's lines included shorter and less discrete lines that did not extend to the pleural surface. The distinct lines were further subdivided into mild, when

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TABLE I

ROENTGEN SIGNS SELECTED FOR ANALYSIS

Roentgen Signs	Definition
1. Kerley's B lines	Fine parallel linear densities in peripheral lung fields (a) Distinct—2 cm. or greater (I) mild—few (II) severe—many (b) Indistinct—short, ill-defined
2. Abnormal pulmonary vascular pattern	Peripheral basilar constriction and central upper dilatation (a) Pure venous (b) Combined venous and arterial
3. Left atrial enlargement	Posterior deviation of the esophagus on the lateral esophagram (I) mild—12 cm.^{2} or less (II) marked—more than 12 cm.^{2}
4. DPA/DHT	MPAP = DPA/DHT × 100
5. Diameter of the right descending pulmonary artery	Measured at the widest point distal to the right middle lobe artery

Abbreviations: DPA = diameter of pulmonary artery; DHT = diameter of the left hemithorax; MPAP = mean pulmonary arterial pressure.

only a few lines were present, and severe indicating the presence of many lines (Fig. 1).

2. ABNORMAL PULMONARY VASCULAR PATTERN

This roentgen sign included both pure venous and combined venous and arterial changes. The changes in the arteries were similar to those in the veins and included constriction of the lower and peripheral vessels and dilatation of the upper and central vessels (Fig. 2–5).

3. LEFT ATRIAL ENLARGEMENT

Left atrial enlargement was defined as any degree of enlargement of the chamber which was detectable on either plain roentgenography of the chest or with the aid of esophagography. The latter method was considered more accurate, and the degree of left atrial enlargement was quantitated by measuring the area of posterior esophageal deviation on the lateral esophagram and expressed in cm.^{2} (Fig. 6). This measurement was obtained in 26 patients. Left atrial size by definition, therefore, implies left atrial enlargement. Marked left atrial enlargement was defined as any degree chamber enlargement that produced more than 12 cm.^{2} of the posterior esophageal deviation.

4. THE RATIO BETWEEN THE DIAMETER OF THE MAIN PULMONARY ARTERY AND THE DIAMETER OF THE LEFT HEMITHORAX (DPA/DHT)

The diameter of the main pulmonary artery was measured on the posteroanterior chest roentgenogram as the distance between the outermost border of the pulmonary artery and the midline of the chest. When the pulmonary artery was straight or slightly concave, the measurement was made from a point on its border midway between the aortic knob and the left atrial appendage. The diameter of the hemithorax was measured from the midline of the chest to the left lateral pleural surface at the level of the left hemidiaphragm. From these measurements, the mean pulmonary arterial pressure (MPAP) was estimated in mm. Hg by the following formula (Fig. 7):

$$MPAP = DPA/DHT \times 100.$$

5. THE DIAMETER OF THE RIGHT DESCENDING PULMONARY ARTERY

This measurement was made on the posteroanterior chest roentgenogram near the first bifurcation of the right descending pulmonary artery at its widest point distal to the origin of the right middle lobe artery. At this level the outer border of the artery was in most cases sharply

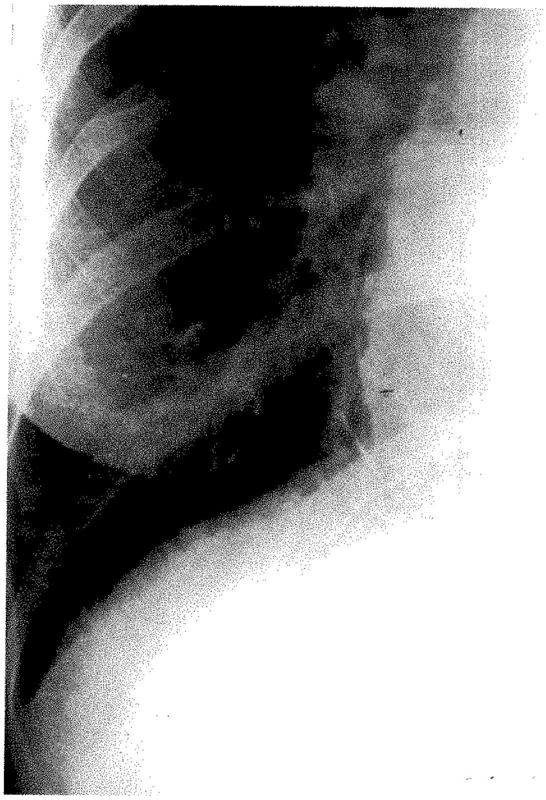


Fig. 1. Kerley's B lines in a patient with operative mitral stenosis (mitral valve area = 0.6 cm.^{2}). Note the many distinct horizontal lines in the right costophrenic sulcus.

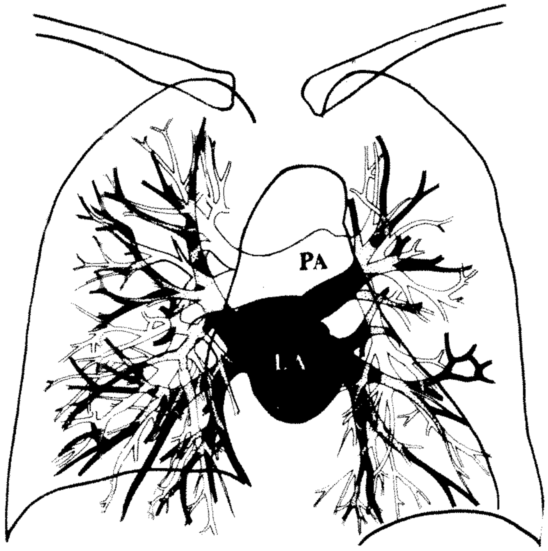


Fig. 2. Composite drawing of arterial and venous phases of a normal pulmonary arteriogram in the supine position. Black images represent the pulmonary veins and white the pulmonary arteries.

outlined against the air-filled lung and the medial border against the air-filled right stem bronchus (Fig. 8).

HEMODYNAMIC DATA

The following hemodynamic data were correlated with the roentgenographic find-

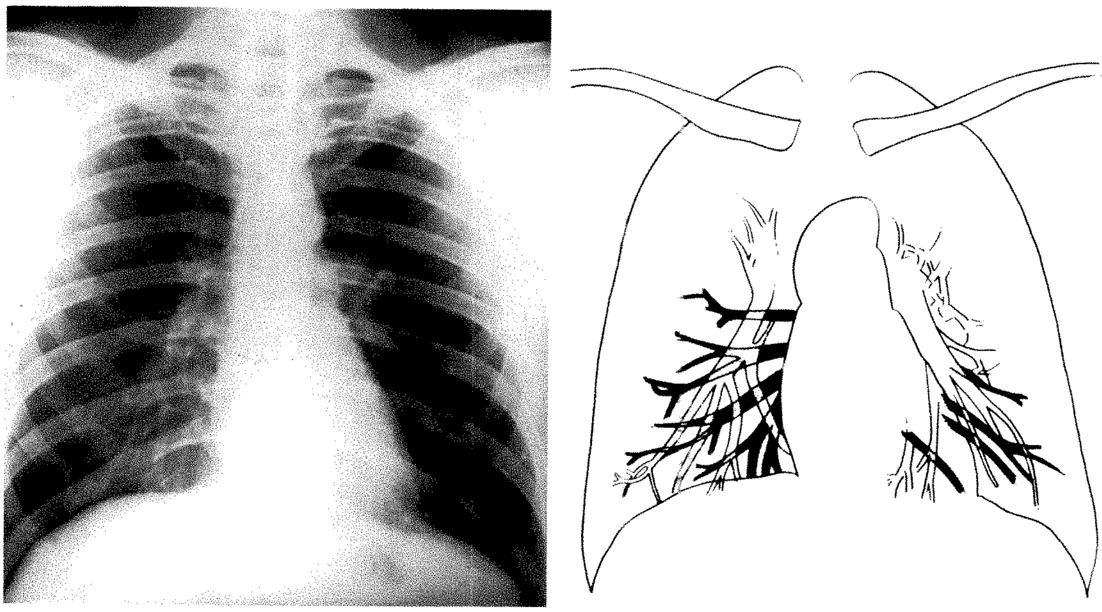
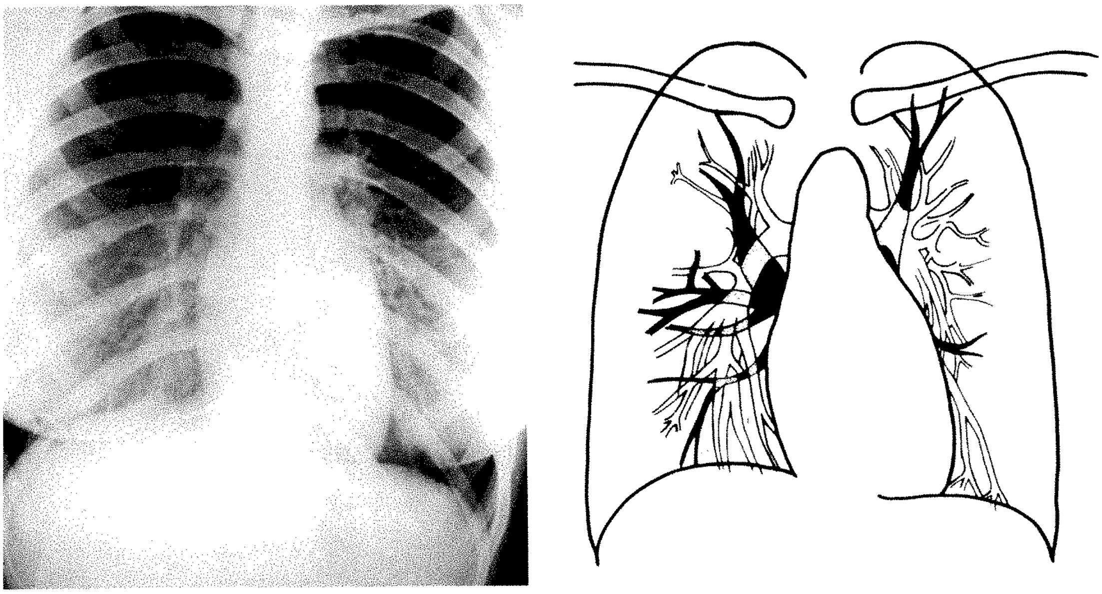


Fig. 3. Normal pulmonary vascular pattern showing larger pulmonary arteries and veins in the lower lung fields.



IG. 4. Pure venous abnormal pulmonary vascular pattern in a patient with nonoperative mitral stenosis (mitral valve area = 1.8 cm.²). Note the dilatation of the upper and the constriction of the lower pulmonary veins. The pulmonary arteries are normal.

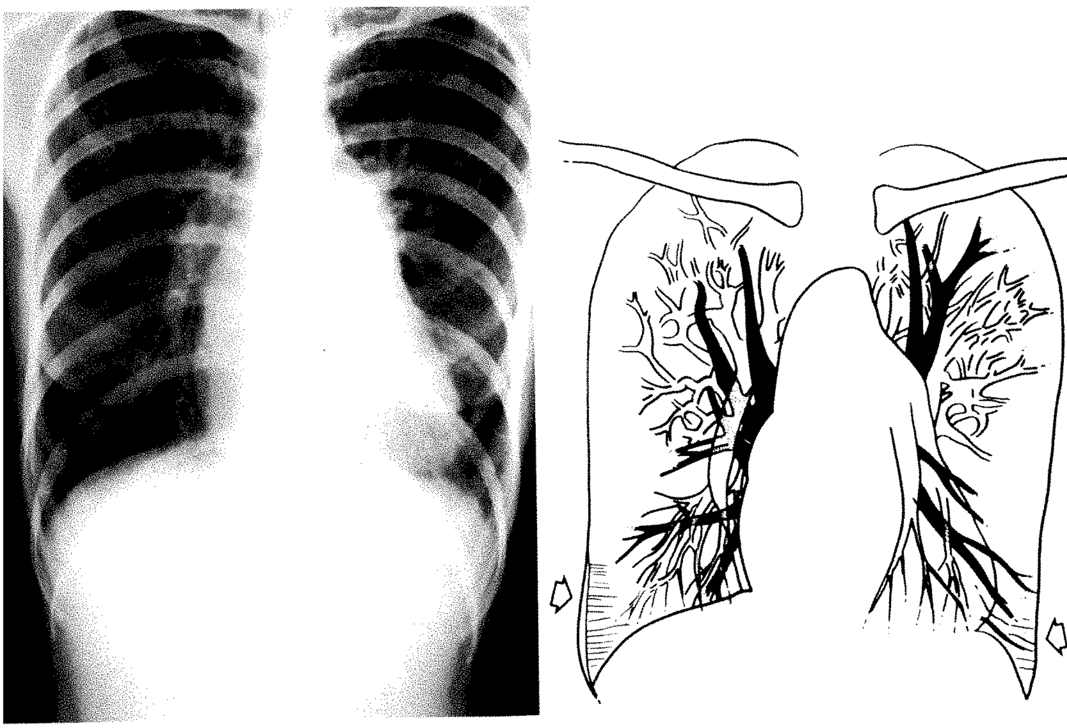


FIG. 5. Combined arterial and venous abnormal pulmonary vascular pattern in a patient with operative mitral stenosis (mitral valve area = 0.7 cm.²). Note the markedly dilated vessels in the upper and the markedly constricted vessels in the lower lung fields. Kerley's B lines are also seen in both costophrenic sulci (arrows).

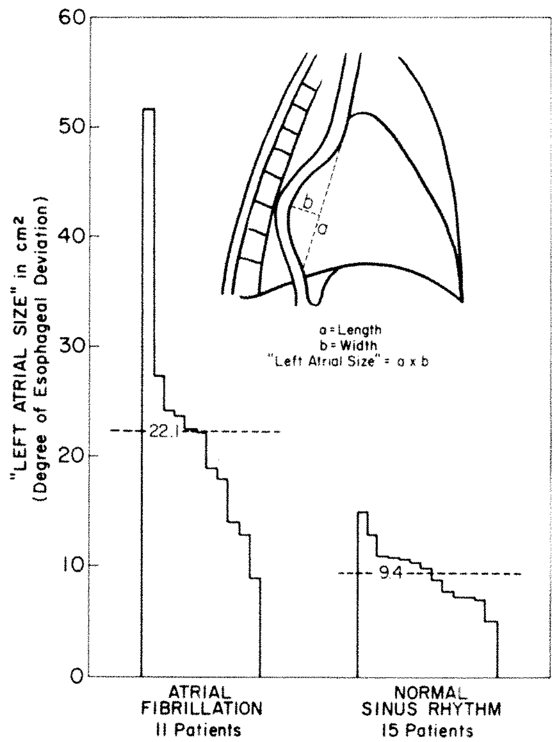


Fig. 6. Relationship of "left atrial size" to atrial fibrillation in patients with mitral stenosis. "Left atrial size" implies the degree of left atrial enlargement in terms of area (cm.²) of posterior deviation of the esophagus in the lateral projection.

ings: Mitral valve area (MVA) calculated in cm.²*; mean pulmonary arterial pressure (MPAP) and mean left atrial pressure (MLAP); total pulmonary resistance (TPR); pulmonary arteriolar resistance (PAR); and left atrial resistance (LAR). The presence of atrial fibrillation (AF) or normal sinus rhythm (NSR) was also noted.

RESULTS

Forty-two of the 60 patients had severe mitral stenosis requiring surgical intervention; MVA of 1.3 cm.² or less. The correlations between the roentgenographic findings and hemodynamic data in all patients are presented.

I. Kerley's B lines (KL)

Distinct Kerley's lines were seen in 23 of the 42 patients (56 per cent) with operative mitral stenosis and in 1 of the 18 nonoperative cases. One of the former had bilateral pleural effusions and was excluded from the statistics involving

* Cases with a calculated MVA of 1.3 cm.² or less were classified as operative mitral stenosis; those with a MVA greater than 1.3 cm.² were considered nonoperative.

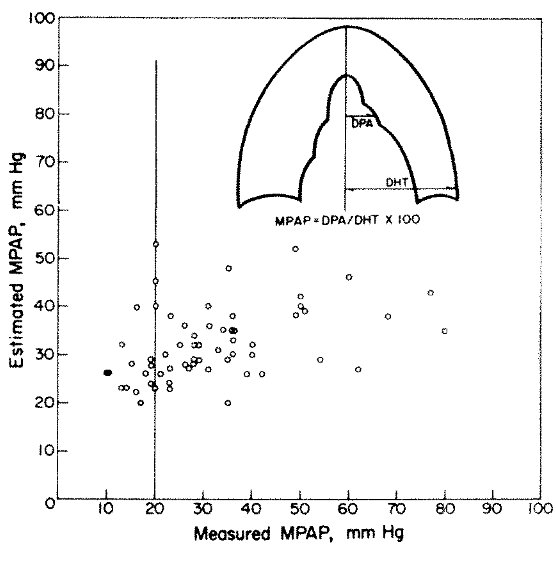


Fig. 7. Relationship of the roentgenographic estimation to the catheterization measurement of the mean pulmonary arterial pressure (MPAP). DPA = diameter of pulmonary artery. DHT = diameter of left hemithorax.

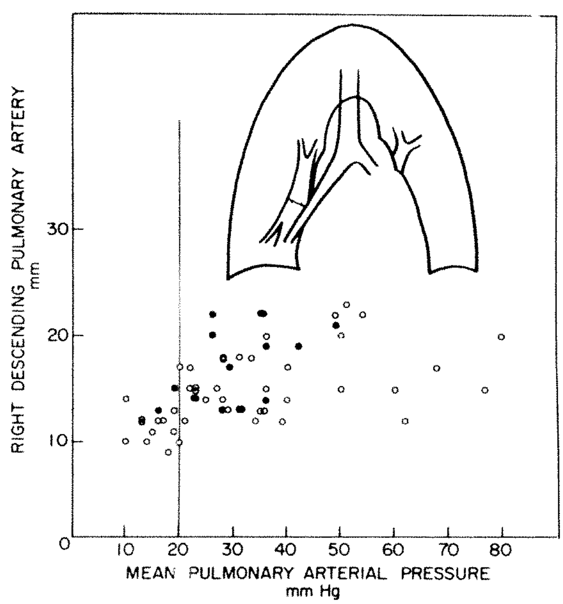


Fig. 8. Relationship of the diameter of the right descending pulmonary artery to the mean pulmonary arterial pressure. ● Male. ○ Female.

TABLE II

CORRELATION OF KERLEY'S LINES AND HEMODYNAMIC DATA IN 59 PATIENTS WITH MITRAL STENOSIS*

A.

Hemodynamic Data		Kerley's B Lines: Absent or Indistinct	Kerley's B Lines: Present
MVA	<1.3 cm.^{2}	18	23
	>1.3 cm.^{2}	17	1
MPAP	>30 mm. Hg	10	18
	<30 mm. Hg	25	6
MLAP	>20 mm. Hg	11	18
	<20 mm. Hg	24	6
TPR	>11 units	5	14
	<11 units	30	10
PAR	>6 units	4	10
	<6 units	31	14
LAR	>5 units	9	18
	<5 units	26	6

B.

Hemodynamic Data		Kerley's B Lines: Absent	Indistinct	Distinct: Few	Distinct: Many
MVA	Range	0.6–2.4	1.0–1.4	0.3–1.2	0.6–1.5
(cm.^{2})	Mean	1.4	1.3	0.8	0.9
MPAP	Range	10–77	19–36	20–80	22–60
(mm. Hg)	Mean	27.1	26.7	39.0	41.4
MLAP	Range	3–32	11–25	13–24	16–32
(mm. Hg)	Mean	15.0	19.0	21.3	23.6
TPR	Range	2.50–26.55	4.32–8.78	6.11–45.33	6.74–23.0
	Mean	7.70	6.20	15.65	13.44
PAR	Range	0.48–15.32	0.8–3.17	2.22–28.0	0.5–12.60
	Mean	3.56	1.84	7.72	5.80
LAR	Range	0.58–11.03	2.73–5.61	3.89–17.33	3.48–17.33
	Mean	4.14	4.36	7.63	7.78

* One out of the 60 patients had bilateral pleural effusion and was excluded from the calculations.

Abbreviations: MVA = mitral valve area calculated by cardiac catheterization; MVA <1.3 cm.^{2} = MVA of 1.3 cm.^{2} or less; MVA >1.3 cm.^{2} = MVA of 1.4 cm.^{2} or more; MPAP = mean pulmonary arterial pressure; MLAP = mean left atrial pressure; TPR = total pulmonary resistance; PAR = pulmonary arteriolar resistance; LAR = left atrial resistance.

Kerley's lines. Twenty-three of the 24 patients (96 per cent) with distinct Kerley's lines had a calculated valve area of 1.3 cm.^{2} or less (Table IIA); in 22 of these patients, the valve area was calculated at 1.1 cm.^{2} or less. The patient in the nonoperative group with distinct Kerley's lines had a MVA of 1.5 cm.^{2} The presence of indistinct lines was of no value in separating operative from nonoperative mitral stenosis (Table IIB).

In patients with distinct lines, the mean pulmonary arterial pressure (MPAP) ranged from 20 to 80 mm. Hg (mean, 40.0); 80 per cent of these patients had a MPAP greater than 30 mm. Hg. The mean left atrial pressure (MLAP) in these patients ranged from 13 to 34 mm. Hg (mean 22.5). The MLAP was greater than 16 mm. Hg in 91 per cent and greater than 20 mm. Hg in 74 per cent of these patients. The presence of indistinct lines was again of no predictive value although such patients had a slightly higher MLAP than patients without Kerley's lines (Table IIB). Those patients with many distinct lines had slightly higher pulmonary arterial and left atrial pressures than those patients with few distinct lines (Fig. 9).

Seventy-five per cent of the patients with Kerley's lines had a left atrial resistance (LAR) greater than 5 units. There was no significant correlation between total pulmonary resistance (TPR) or pulmonary arteriolar resistance (PAR) and the presence of Kerley's lines; however, in patients without Kerley's lines the TPR, PAR and LAR were within normal limits in 84, 87 and 74 per cent, respectively.

2. ABNORMAL PULMONARY VASCULAR PATTERN (AVP)

There was no correlation between a pure venous abnormal pulmonary vascular pattern (AVP) and the calculated

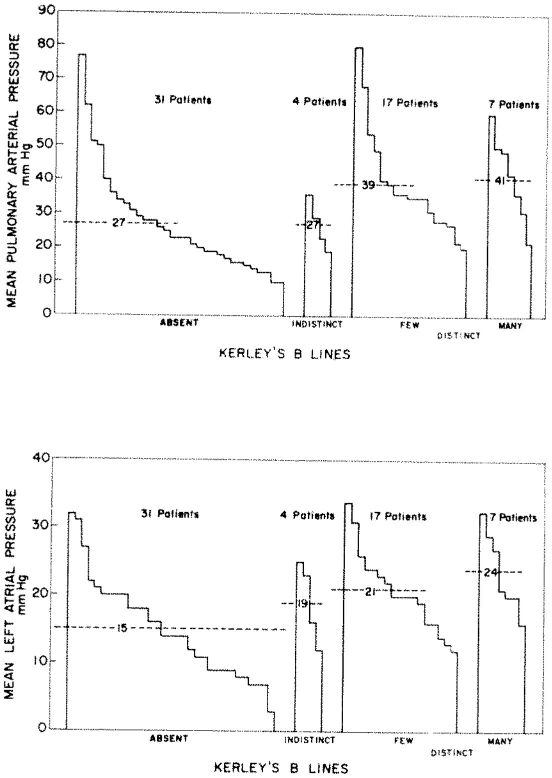


Fig. 9. *Upper:* Relationship of Kerley's B lines to mean pulmonary arterial pressure. The horizontal broken line indicates the average value of the pressure in each group of patients. *Lower:* Relationship of Kerley's B lines to mean left atrial pressure. The horizontal broken line indicates the average value of the pressure in each group of patients.

mitral valve area. However, 33 of the 34 patients with both combined venous and arterial changes had operative mitral stenosis (Table IIIA). Twenty-six of these 33 patients (78 per cent) had a calculated mitral valve area of 1.1 cm.^{2} or less.

With the development of more severe pulmonary vascular changes, *i.e.*, normal→pure venous AVP→combined venous and arterial AVP, a progressive increase was observed in mean pulmonary arterial pressure, mean left atrial pressure, and total pulmonary and left atrial resistance (Table IIIB). A significant elevation in pulmonary arteriolar resistance (PAR) was noted in patients with combined arterial and venous changes but not in those with pure venous changes.

3. Left atrial enlargement (LAE)

Enlargement of the left atrium was observed in 58 of the 60 patients. There was a distinct relationship between marked left atrial enlargement and the presence of atrial fibrillation. The average area of posterior esophageal deviation in 11 patients with atrial fibrillation was 22.1 cm.^{2}, and 9.4 cm.^{2} in 15 patients with normal sinus rhythm (Fig. 6). Eighty-eight per cent of the patients with an area greater than 12 cm.^{2} had atrial fibrillation. Of the patients in atrial fibrillation, 87.5 per cent were in the operative and 12.5 per cent in the nonoperative group (Table IV). In those patients with greater than 12 cm.^{2} of esophageal deviation, 83 per cent had a mitral valve area of 1.3 cm.^{2} or less (Table VII). This measurement, although indirect, was therefore useful in predicting operative mitral stenosis (Fig. 10). There were no other consistent correlations between left atrial size and the hemodynamic data.

4. Ratio between the diameter of the main pulmonary artery and the diameter of the hemithorax (DPA)/(DHT)

This ratio provided estimates of the mean pulmonary artery pressure within 20 per cent of the pressure determined at catheterization in 32 of the 60 patients and within 30 per cent in 37 patients (Fig. 7).

The data obtained in 14 normal subjects are included in Table V. The ratio of DPA and DHT tends to overestimate the pulmonary artery pressure in normal subjects and in patients with mild mitral stenosis, and to underestimate the pressure in patients with operative or severe mitral stenosis.

5. Diameter of the right descending pulmonary artery (DRPA)

DRPA measurements in normal subjects and in 60 patients with mitral stenosis are shown in Table VI. The values

TABLE III

CORRELATION OF ABNORMAL PULMONARY VASCULAR PATTERN AND HEMODYNAMIC DATA IN 60 PATIENTS WITH MITRAL STENOSIS

A.	Hemodynamic Data	Pulmonary Vascular Pattern: Normal	Abnormal: Pure Venous	Abnormal: Venous and Arterial	B.	Hemodynamic Data	Pulmonary Vascular Pattern: Normal	Abnormal: Pure Venous	Abnormal: Venous and Arterial
MVA	<1.3 cm.^{2}	4	5	33	MVA	Range	0.7–2.4	0.7–2.1	0.3–1.5
	>1.3 cm.^{2}	8	9	1	(cm.^{2})	Mean	1.6	1.4	0.86
MPAP	>30 mm. Hg	1	5	22	MPAP	Range	13–31	10–77	20–80
	<30 mm. Hg	11	9	12	(mm. Hg)	Mean	25.0	28.0	38.4
MLAP	>20 mm. Hg	0	5	22	MLAP	Range	7–18	3–32	12–34
	<20 mm. Hg	12	9	12	(mm. Hg)	Mean	10.7	15.5	21.3
TPR	>11 units	1	1	17	TPR	Range	3.09–14.73	2.38–26.55	5.8–45.33
	<11 units	11	13	17		Mean	6.44	7.51	14.20
PAR	>6 units	1	1	12	PAR	Range	0.54–7.89	0.48–15.52	0.5–28.0
	<6 units	11	13	22		Mean	3.90	3.42	6.26
LAR	>5 units	1	2	28	LAR	Range	1.23–3.60	0.58–11.03	1.46–17.33
	<5 units	11	12	6		Mean	3.1	4.10	7.19

Abbreviations as in Table I and II.

are significantly higher in patients with mitral stenosis than in normal subjects. Furthermore, among the patients a greater mean value is noted in those with severe mitral stenosis.

In male patients with mitral stenosis, a DRPA of 16 mm. or more indicated the presence of pulmonary hypertension; the corresponding diameter in the female was 15 mm. (Fig. 8). On the other hand, the presence of pulmonary hypertension could be virtually excluded with DRPA measurements of 11 and 12 mm. or less in female and male patients, respectively. Intermediate DRPA measurements were of no use in predicting the presence of pulmonary hypertension.

ACCURACY OF THE ROENTGENOGRAPHIC SIGNS IN PREDICTING OPERATIVE MITRAL STENOSIS

The roentgenographic demonstration of combined venous and arterial pulmonary vascular changes, Kerley's B lines, and marked left atrial enlargement indicates the presence of operative mitral stenosis (1.3 cm.^{2} or less) in 97 per cent, 96 per cent,

TABLE IV

INCIDENCE DISTRIBUTION OF ATRIAL FIBRILLATION IN OPERATIVE AND NONOPERATIVE CASES OF MITRAL STENOSIS

MVA	AF	NSR	Total
<1.3 cm.^{2}	21	21	42
>1.3 cm.^{2}	3	15	18
Total	24	36	60

Abbreviations: AF = atrial fibrillation; NSR = normal sinus rhythm; MVA <1.3 cm.^{2} = MVA of 1.3 cm.^{2} or less; MVA >1.3 cm.^{2} = MVA of 1.4 cm.^{2} or more.

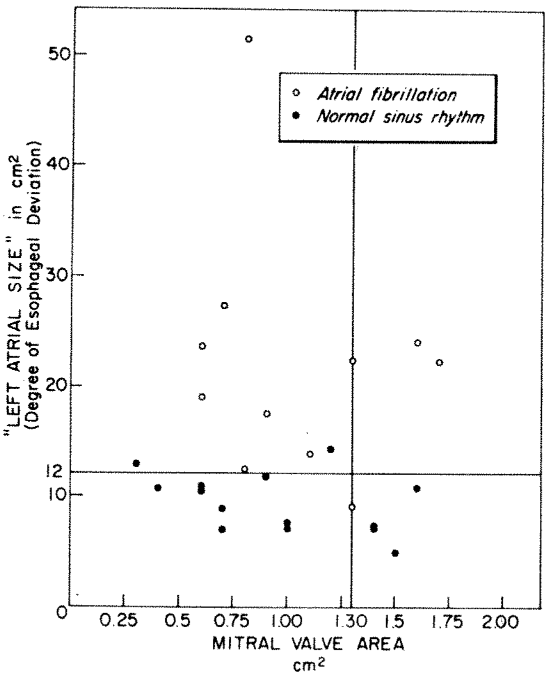


Fig. 10. Relationship of "left atrial size" to mitral valve area in patients with atrial fibrillation and normal sinus rhythm.

and 83 per cent of the patients, respectively (Table VII). Operative mitral stenosis was present in 100 per cent of the patients with the roentgenographic combination of Kerley's B lines and/or combined arterial and venous pulmonary vascular changes plus marked left atrial enlargement. However, in the absence of these roentgenographic signs tight mitral stenosis could not be excluded.

DISCUSSION

The hemodynamic changes of progressive mitral stenosis have been classified as passive and reactive. Rushmer[20] has reported that a progressive reduction in mitral valve area is accompanied by a passive increase in left atrial pressure. This passive increase in distending pressure is, therefore, probably responsible for the gradual increase in left atrial size seen roentgenographically. As the pulmonary vasculature is in direct continuity with the left atrium, this increase in pres-

Table V

MEAN VALUES OF ESTIMATED AND MEASURED MPAP IN NORMAL SUBJECTS AND IN PATIENTS WITH MITRAL STENOSIS

Estimated MPAP (mm.Hg) (DPA/DHT×100)			Measured MPAP (mm.Hg) (Catheterization Data)		
Normal*	Nonoperative MS	Operative MS	Normal†	Nonoperative MS	Operative MS
22.7	27.6	33.7	16.0	20.3	37.2

* Mean value obtained from 14 normal subjects (7 males and 7 females).
† Mean value in normal subjects according to Schlant.
Abbreviations: MS = mitral stenosis; MPAP = mean pulmonary arterial pressure; DPA = diameter of main pulmonary artery; DHT = diameter of the hemithorax.

Table VI

DIAMETER OF THE RIGHT DESCENDING PULMONARY ARTERY

Normal Subjects*		Patients with Mitral Stenosis			
		Nonoperative		Operative	
Males	Females	Males	Females	Males	Females
13.0 (11–15) mm.	12.0 (10–14) mm.	14.8 (13–17) mm.	12.6 (9–18) mm.	18.1 (13–22) mm.	16.0 (10–23) mm.

* Values obtained from 14 normal subjects (7 males and 7 females).

Table VII

ACCURACY OF ROENTGENOGRAPHIC SIGNS IN DISTINGUISHING BETWEEN OPERATIVE AND NONOPERATIVE MITRAL STENOSIS

MVA	Roentgenographic Signs	Cases Examined	Roentgenographic Estimation: Operative No. of Cases	Operative Per Cent	Nonoperative No. of Cases	Nonoperative Per Cent
	KL	59				
<1.3 cm.²			23	96	19	66
>1.3 cm.²			1	4	16	34
	CAVP	60				
<1.3 cm.²			33	97	9	17
>1.3 cm.²			1	3	17	83
	MLAE	26				
<1.3 cm.²			10	83	10	54
>1.3 cm.²			2	17	4	46
	KL+MLAE	26				
<1.3 cm.²			7	100	13	68
>1.3 cm.²			0	0	6	32
	CAVP+MLAE	26				
<1.3 cm.²			6	100	14	70
>1.3 cm.²			0	0	6	30
	KL+CAVP+MLAE	26				
<1.3 cm.²			6	100	14	70
>1.3 cm.²			0	0	6	30

Abbreviations: MVA= mitral valve area calculated by cardiac catheterization; MVA<1.3 cm.²= MVA of 1.3 cm.² or less; MVA >1.3 cm.²= MVA of 1.4 cm.² or more; KL= Kerley's B lines; CAVP= combined venous and arterial abnormalities in the pulmonary vascular system; MLAE= left atrial enlargement to more than 12 cm.².

sure is transmitted to the right side of the heart with the production of pulmonary congestion. These changes are reflected roentgenographically by the generalized dilatation of the pulmonary arteries and veins until "reactive" changes develop in the pulmonary vasculature. In addition, engorgement of the pulmonary veins and lymphatics leads to the development of Kerley's lines which are thought to represent thickened interlobular septa from interstitial edema and/or fibrosis.[4,6,7,10,11,19] Kerley's lines are usually seen as thin parallel linear densities, perpendicular to a pleural surface in the periphery of the lung. In order for these thin lines to be visualized, according to Ellis,[4] they must be oriented parallel to the roentgen-ray beam. This optimal orientation of the interlobular planes occurs in the costophrenic sulci. Such lines are designated as "B" lines. Kerley's lines may also be seen radiating toward the hilar regions for a distance of 2 inches or more without branching. These lines are designated as "A" lines. Kerley's A lines are seen only with acute episodes of pulmonary interstitial edema and are always transient. Therefore, only "B" lines are present long enough to be clinically useful.[4,11]

As the pulmonary capillary pressure approaches plasma osmotic pressure, "reactive" changes occur in the pulmonary vasculature in an attempt to protect the pulmonary capillary bed and to prevent the development of pulmonary edema. Many descriptions of these changes have been reported.[2,4,11,13,14,17,28] Peripheral constriction begins initially in the pulmonary veins with later involvement of the pul-

monary arteries. Friedman and Braunwald[5] and other investigators[3,26] have studied regional pulmonary blood flow in normal subjects as well as patients with mitral stenosis by means of radioisotope techniques. These studies have demonstrated that flow to the lower lung fields is normally increased in the erect position. In patients with mitral stenosis, however, a reversal of this pattern was observed with more flow to the upper lobes than to the lower lobes. These investigators concluded that the increased hydrostatic pressure exerted on the vasculature to the lower lungs made them more responsive to these changes. Ueda and co-workers[26] have demonstrated that this reversal of flow in patients with mitral stenosis may be even more abnormal in the supine position. Changes in flow, therefore, appear to be responsible for the abnormal pulmonary venous and arterial changes observed on the plain roentgenogram of the chest.

As has been demonstrated in this study and in reports by other investigators, both the left atrium and the main pulmonary artery enlarge with the development of greater distending pressures. We have demonstrated the ability to estimate, with reasonable accuracy, the distending pressure in the mean pulmonary artery pressure by means of DPA/DHT and the diameter of the right descending pulmonary artery. However, left atrial size did not reflect mean left atrial pressure with any degree of reliability. Melhem *et al.*[16] have suggested several reasons for the latter: (1) difficulty in accurately assessing left atrial size by chest roentgenography; (2) the development of pulmonary arteriolar constriction; and (3) pathophysiologic changes in atrial compliance. Such changes in compliance apparently do not occur in the pulmonary artery until the development of pulmonary sclerosis secondary to long standing hypertension. Therefore, the size of the pulmonary artery remains a good indicator of pressure until the late stages of mitral stenosis. In addition, the influence of body size is partially compen sated for by the use of the hemithoraci diameter in the calculation.[12,16,17,25] It i apparent that the distance from the mid sternum to the outer border of the pul monary artery is not a measure of th diameter of the pulmonary artery. B measuring the true diameter of this vess or its right main branch on a pulmonar angiogram, Soloff *et al.*[25] and Sidd *et al.* were able to more accurately estimate th mean pulmonary artery pressure.

Although left atrial size did not appea to be related to left atrial pressure, ther was a definite association with the presenc of atrial fibrillation. The pathophysiolog of this relationship is still unresolved. I has been postulated that the large lef atrium in mitral stenosis is more suscep tible to fibrillation, while others sugges that as the atrium fibrillates it enlarge secondary to a loss of muscle tone. Fur thermore, the massive loss of myocardiun of the left atrium incident to the initia rheumatic process might be the single mos important factor in the development c marked left atrial enlargement and atria fibrillation in tight mitral stenosis.[16,

It is apparent from this study that al though the roentgenographic measure ment of chamber or vessel size may be c use in estimating its distending pressure it is frequently fraught with difficulty However, the use of certain of these sign and combinations thereof, has prove extremely helpful and accurate in dis tinguishing between operative or sever from nonoperative or mild mitral stenosis

SUMMARY

In 60 patients with pure mitral stenosis roentgenographic examinations of the ches were made within 30 days of complet right and left heart catheterization. Th relative accuracy of the different roentge signs in predicting a mitral valve area c 1.3 cm.^{2} or less was as follows: (1) Kerley B lines—96 per cent; (2) combined veno and arterial abnormalities in the pulmonar vascular pattern—97 per cent; (3) lef

atrial enlargement producing more than 12 cm.[2] posterior deviation of the esophagus—83 per cent; (4) either 1 or 2 plus 3—100 per cent. Marked left atrial enlargement correlated best with atrial fibrillation. For assessing pressures and the resistances, the abnormal pulmonary vascular pattern appeared to be more sensitive than Kerley's B lines. In predicting mean pulmonary arterial pressure, the pulmonary artery/hemithorax ratio was more accurate than the diameter of the right descending pulmonary artery.

It is concluded that in addition to indicating specific hemodynamics, chest roentgenograms provide a sensitive and accurate means of predicting the presence of severe or operative mitral stenosis.

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LEFT ATRIAL CALCIFICATION*

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CALCIFICATION in the wall of the left atrium is almost always a result of rheumatic heart disease with predominant involvement of the mitral valve. Mitral stenosis with significant insufficiency, atrial fibrillation, and mural thrombi are characteristically associated with the intramural calcification. Seltzer *et al.*[7] found thrombotic material in the left atrium in 13 of 15 patients with left atrial calcification.

In 1898, Claude and Levaditi[2] noted a focal area of calcification in the left atrium of a 19 year old girl at necropsy. However, the first case of left atrial calcification diagnosed *in vivo* by roentgenologic methods was not recorded until 1933.[1]

A review of 1,826 cases of mitral valvular disease diagnosed at the University of Minnesota Hospitals during the years 1951 through 1964 yielded 26 patients with roentgenologic evidence of left atrial calcification. The purpose of this paper is to present an analysis of this group of patients.

FINDINGS

The incidence of left atrial calcification in patients with mitral stenosis with or without insufficiency was approximately 0.5 per cent in our series. There were 5 males and 21 females, a distribution similar to that seen in other studies, and one which reflects the well known female predominance of cases of mitral valvular disease. The mean age at the time of diagnosis of left atrial calcification was 45 years.

Of the 26 patients whose roentgenograms showed densities suggesting calcification, 13 were proven at surgery or autopsy to have left atrial wall calcification. An additional 9 patients underwent surgery, but the surgeon made no mention on the operative report of calcification of the left atrium. The remaining 4 cases did not come to surgery or autopsy. Thus the roentgen diagnosis was verified in exactly one-half of the total group. Calcification in the mitral valve leaflets was identified at surgery or necropsy in 12 of the 26 cases, a finding which differs considerably from the relatively low incidence (20 per cent) cited in the series of Seltzer *et al.*[7]

While thrombus in the left atrium is a frequent concomitant of mural calcification, histologically proven calcification in the thrombus is unusual. Calcium within a thrombus was verified by the pathologist in only 3 of our cases. The roentgenographic pattern of calcification in these patients did not differ from the remainder of the group.

Calcification in the wall of the left atrium is frequently first identified at fluoroscopy. Well penetrated roentgenograms will often verify this finding. Planigraphy will yield the best visual appraisal of the extent and location of the calcification (Fig. 1). Kymography was frequently performed for appraisal of these patients, but was useful mainly in recording the pulsations of the cardiac borders.

Three roentgenographic patterns of left atrial calcification were identified:

The first and most common pattern was that of a group of rim-like plaques of density projected over the mid portion of the heart. This pattern was most frequently seen superiorly and posteriorly (Fig. 2, *A* and *B*). These thin curvilinear densities were noted in 16 of the 26 cases.

A second pattern—groups of shaggy nodular calcifications giving a laminated appearance—was seen in an additional 4 patients. Only 1 of these patients proved to have calcification in a thrombus. The

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FIG. 1. Planigram showing laminated calcification.

shaggy calcifications in the other 3 cases a apparently due to irregular deposition small plaques of calcium within the le atrial wall itself (Fig. 3).

The third pattern of a dense circun ferential shell of calcium projected over tl center of the cardiac silhouette was seen only 2 patients.

The remaining 4 cases of left atrial ca cification were identified only at fluoro copy and not roentgenographically. Pla roentgenograms of these patients we rather underpenetrated, emphasizing tl importance of high kilovoltage well pen trated roentgenograms in making tl diagnosis.

DISCUSSION

The finding of calcification in the wall the left atrium has considerable clinic significance. Extensive calcification ma impose several technical limitations upc the surgeon in his operative approach the mitral valve.[5] The frequent associatic

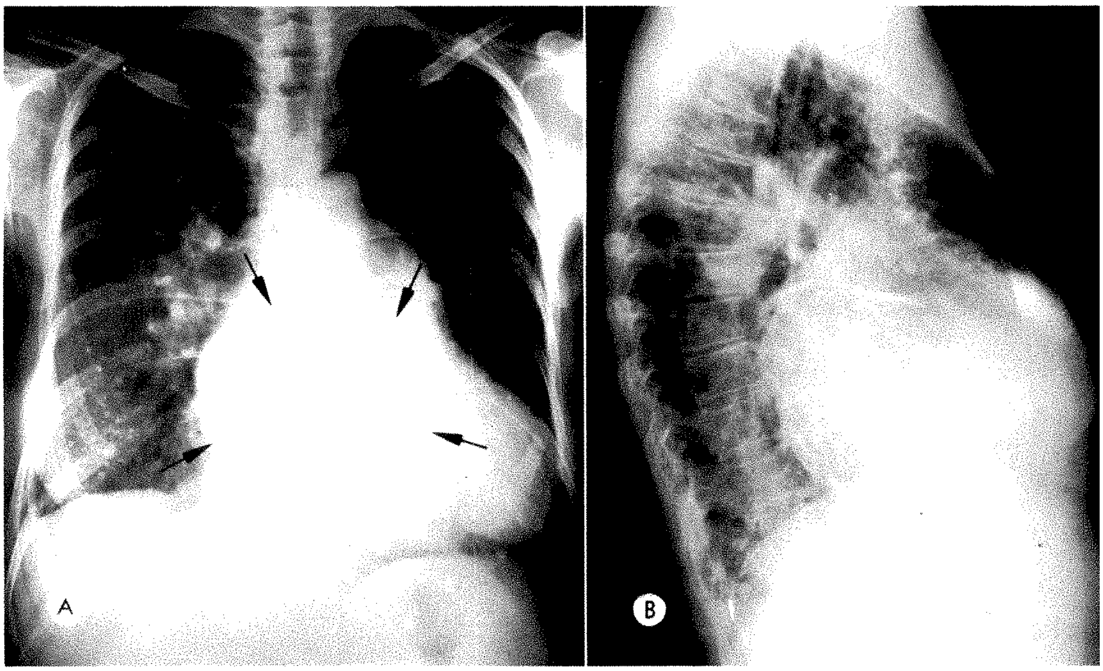

FIG. 2. (*A*) Posteroanterior roentgenogram of a 41 year old female with mitral valve lesion showing calcific tion in the left atrial wall (arrows), and pulmonary ossifications. (*B*) Lateral roentgenogram of sa patient.

of left atrial thrombus with extensive mural calcification raises the hazard of fragmentation during surgery, resulting in embolization.[4] It is, therefore, of considerable importance that the roentgenologic diagnosis be accurate with regard to the extent and location of these calcifications. Well-penetrated roentgenograms and image amplified fluoroscopy may demonstrate thin curvilinear calcific densities over the center of the heart in the frontal view. In lateral and oblique projections, the calcification frequently outlines the posterior wall of the left atrium. We have been impressed by the proximity of these calcifications to the barium-filled esophagus. Therefore, we feel that a well-penetrated left anterior oblique roentgenogram without barium in the esophagus should be taken, so that curvilinear streaks of barium in the esophagus are not confused with calcifications in the posterior wall of the left atrium.

Left atrial wall calcifications are superficial involving endocardium and superficial layers of the muscle. The authors do not support the theory that active rheumatic inflammation accounts for the calcification. We believe that mitral stenosis is the dominant lesion and local tissue necrosis and eventually calcifications may be due to overstretching of the atrial wall.[3]

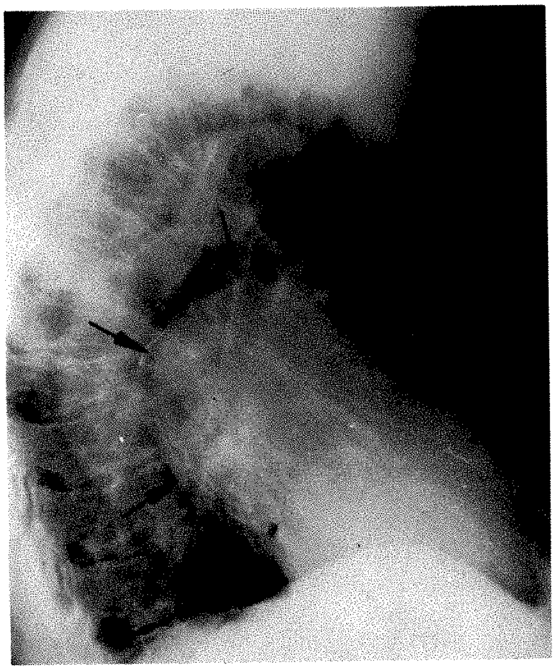

Fig. 3. Lateral roentgenogram of a 52 year old male with mitral valve lesion showing shaggy nodular calcification of left atrial wall (arrows).

Fig. 4. Roentgenogram of autopsy specimen showing calcifications of the wall of the left atrium.

Calcification in a left atrial thrombus is an unusual finding in our series and cannot be differentiated roentgenologically from irregular deposition of calcium in the wall, since both present with a shaggy nodular laminated pattern (Fig. 4 and 5).

Left atrial wall calcification has been described in patients on massive doses of vitamin D or with metabolic calcinosis, but these cases are very rare and do not present the pattern of curvilinear rim-like

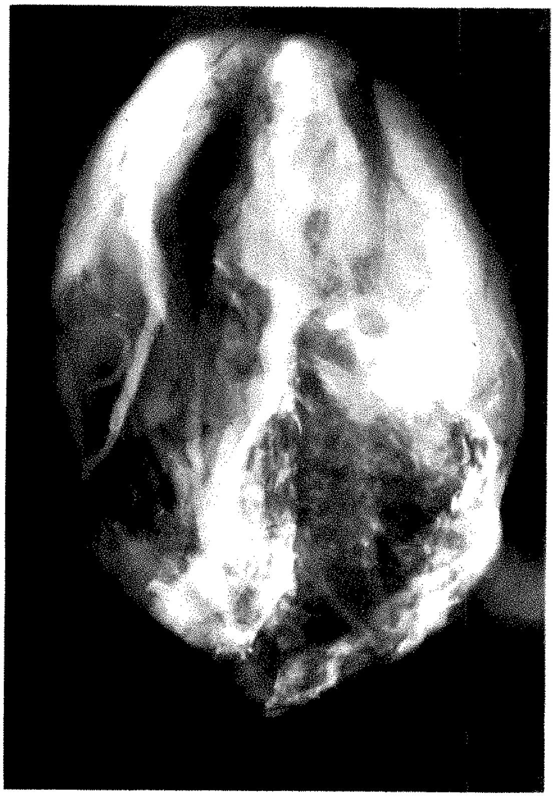

FIG. 5. Roentgenogram of autopsy specimen showing dense calcification in the wall of the left atrium.

calcification which was most typical of this series of patients with mitral disease.[6]

The differential diagnosis of left atrial calcification would include calcification in coronary arteries, ventricular aneurysms, diseased cardiac valves, pericardium, ventricular infarctions, endocardial tumors, hilar lymph nodes, and costal cartilages.[8,9]

The location and motion usually establish the diagnosis. The calcifications in the left atrial wall are quite characteristic, corresponding to the outline of left atrium. Good basic knowledge of anatomy and topography of the cardiac chambers, valves and coronary arteries is, of course, essential in analyzing cardiac calcifications.

CONCLUSIONS

A review of 1,826 cases of mitral stenosis and/or insufficiency seen at the University of Minnesota Hospitals in a 14 year period yielded 26 patients with roentgenologic evidence of calcification in the wall of the left atrium. Thirteen were verified at surgery or necropsy.

Identification and location of left atrial calcification is of considerable clinical importance. Typically, fluoroscopy and well-penetrated roentgenograms reveal curvilinear rim-like densities projected over the center of the heart and best identified on the superior and posterior margins of the heart shadow in the frontal and left anterior oblique projections.

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PERISPHERICAL CALCIFICATION AT THE SITE OF OLD MYOCARDIAL INFARCTION*

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DYSTROPHIC myocardial calcification is uncommon and its mechanism obscure.[6] Its occurrence at the site of myocardial infarction is very unusual. The author reports a case which demonstrated roentgenographically a perispherical (as in the wall of a cyst) calcification at the site of an old myocardial infarction. There have been only 12 similar cases previously reported.

REPORT OF A CASE

Mrs. C.B.C., a 55 year old widow and former U. S. Army nurse, entered the U. S. Public Health Service Hospital at Baltimore, Maryland because of shortness of breath and cough. She had had chronic and recurrent acute bronchitis since early adult life. Thirteen years before admission, she suffered a well documented acute myocardial infarction and was treated for several weeks at another hospital. Chest roentgenography at this time did not show cardiac calcification. She had had no symptoms suggestive of coronary artery disease since that time. Occasional evening ankle edema had developed in recent years. As the wife of an Army officer, she had traveled widely in this country and had lived abroad on two occasions: the Philippine Islands from 1922 to 1924; and Panama from 1931 to 1934. She had had a dog in her home frequently, even when overseas, but these had all been born and bred in the United States. Cigarettes and alcohol had been used in moderation for many years. She had never been pregnant. There was no history of chest trauma. Except for her respiratory illnesses and myocardial infarction, she had been well. On physical examination, the findings were limited to the respiratory and cardiovascular systems. At rest, the patient was mildly tachypneic and expiration was prolonged. The anteroposterior diameter of the chest was increased and, on percussion, the diaphragm was found to be relatively low in position and limited in excursion. On auscultation, the breath sounds were rough, and wheezing was heard throughout expiration. Coarse ronchi were heard over the entire chest and transient fine rales were heard at the lung bases. The neck veins were prominent but filled only to the supraclavicular region in the sitting position. Arterial pressure was 105/70 mm. Hg and heart rate 68 beats per minute. The heart was of normal size and shape. The sounds were distant; aortic and pulmonary second sounds were of equal intensity and "split" normally with respiration; no murmurs were heard. Examination of the abdomen was negative. Pedal pulses were not palpable; peripheral arteries were firm on palpation. There was no edema.

Routine urinalysis, hemoglobin and hematocrit determinations were within normal limits. Serologic tests for syphilis were negative. Blood chemistries in milligrams per cent were as follows: fasting blood sugar, 81: urea nitrogen, 9: cholesterol, 235; calcium, 10.2; phosphorus 4.2. Serum total protein was 7.1 gm. per cent with an albumin-globulin ratio of 4.5/2.6. The alkaline phosphatase level was 3.0 Bodansky units. Serum sodium, potassium and chloride were within normal limits, and the basal metabolism rate was normal. On admission, the venous pressure was 110 mm. of saline. Vital capacity was 1,242 cc. and maximum breathing capacity was 40 liters/min. (both significantly below normal levels); there was evidence of "air trapping" on the spirographic tracing. Tuberculin skin tests (1:1,000 and 1:100) were negative. Echinococcus (hydatid) skin test (with known potent antigen) was negative; the Echinococcus complement fixation test (performed by the Communicable Disease Center, U. S. Public Health Service) was negative. Serial electrocardiograms showed no change and were very similar to those recorded following her acute infarction 13 years previously (Fig. 1). All deflections were of low amplitude, but for the P-waves which were relatively tall. Right axis deviation was associated with QS waves in leads V 1–3, rS waves in

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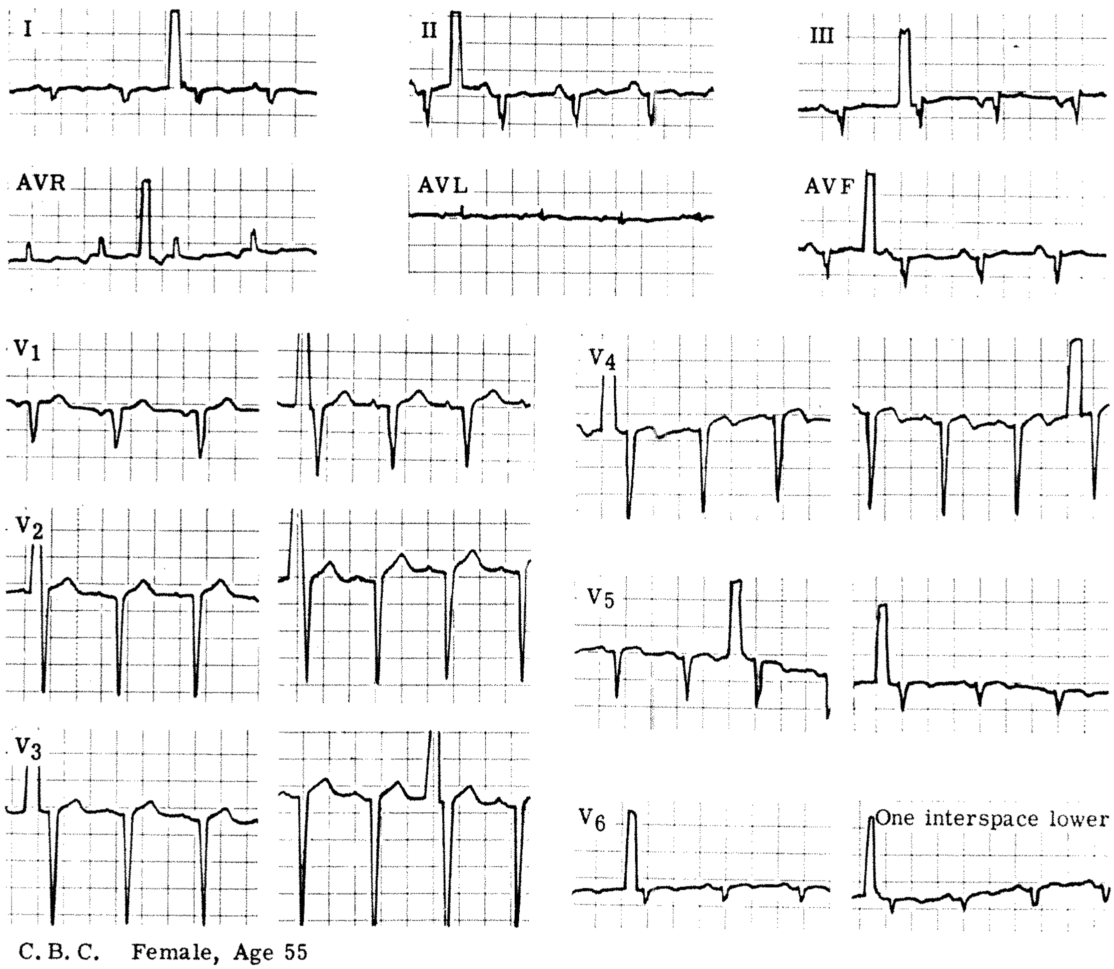

FIG. 1. Electrocardiogram consistent with chronic lung disease and old myocardial infarction. The unmarked tracings, paired with labeled chest-lead tracings, were recorded from electrode positions, one interspace below the usual electrode locations. The tracing is overstandardized because of low voltage.

V 4-6, and slight ST-segment elevation and T wave inversion in V 4-6.

Roentgen examination of the chest showed the lung fields to be clear with slightly increased radiolucency; the diaphragm was low in position. The heart was of normal size and the aorta and pulmonary vessels appeared normal. A near circular calcified mass 3.5 cm. in diameter was observed within the cardiac apex on the posteroanterior projection (Fig. 2*A*). Its persisting circular shape in the lateral and oblique projections (Fig. 2*B*) gave it the appearance of calcification in the wall of a cystic structure. A special spot roentgenogram revealed irregular areas of calcification within the outlines of the perispherical calcification (Fig. 3). On fluoroscopy, the entire mass was seen to move synchronously with the movements of the left ventricular border.

Routine asthmatic measures and antibiotics brought about significant improvement in her respiratory symptoms. After 12 days, she was discharged from the hospital and was followed subsequently as an out-patient. She continued to suffer from chronic respiratory symptoms and occasional respiratory infections. Roentgenographic and fluoroscopic findings had not changed 8 months following discharge, when she was lost to follow-up. Subsequent search revealed that she had died suddenly 5 years after the study, following several months of chronic, progressive congestive heart failure, and symptoms of coronary artery disease. Autopsy was not performed.

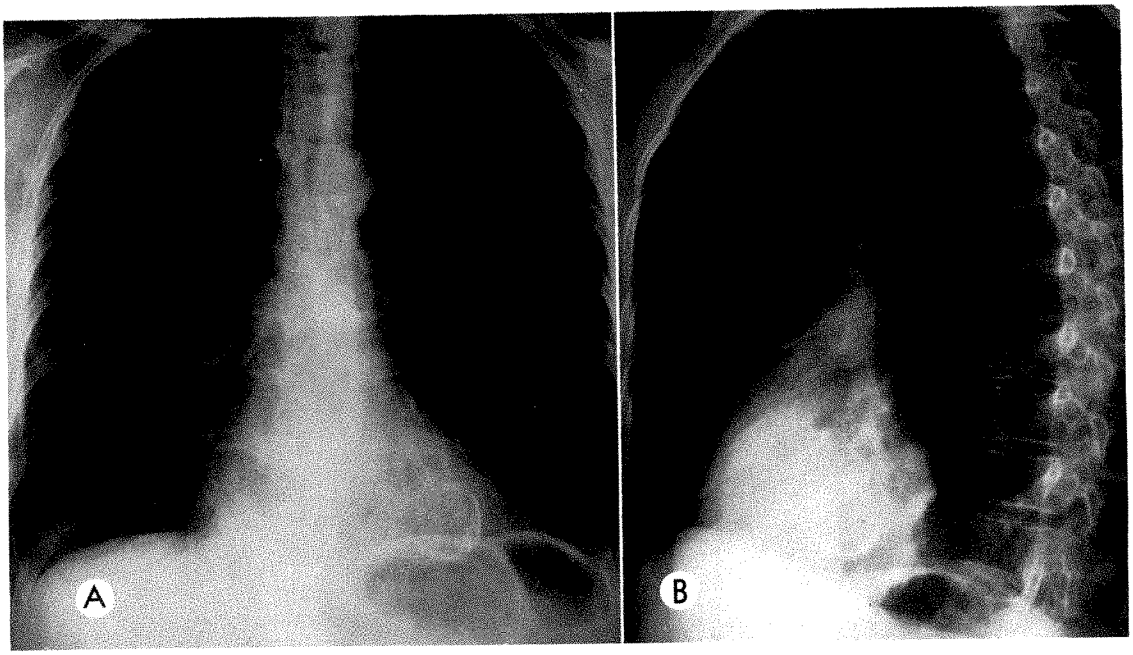

FIG. 2. Perispherical calcification within the left ventricle. (*A*) Posteroanterior projection. (*B*) Oblique projection.

DISCUSSION

Calcification at the site of myocardial infarction may occur as an amorphous intramyocardial mass, within a mural thrombus or, as is most common, within the wall surrounding an infarcted area. Brean *et al.*[5] performed roentgenography routinely at autopsy in a series of 813 cases and discovered 5 cases with gross calcification at the site of old myocardial infarction (0.6 per cent). These represented 7.6 per cent of all old myocardial infarctions in their series. All 5 cases were found among a group of 29 "large" infarctions, an instance of 17.2 per cent. From the information in the literature and in their own cases, they concluded that calcification does not occur at the site of myocardial infarction until at least 6 years after the acute infarction, and that the lesion is usually found only in elderly men; they found no case in a woman, although they described one probable case under observation at that time. Bogoch and Christopherson[4] have described a case in which calcification was seen to develop and increase rapidly in size over a period of months. Near complete calcification of the cyst-like wall surrounding a healed myocardial infarction has been de-

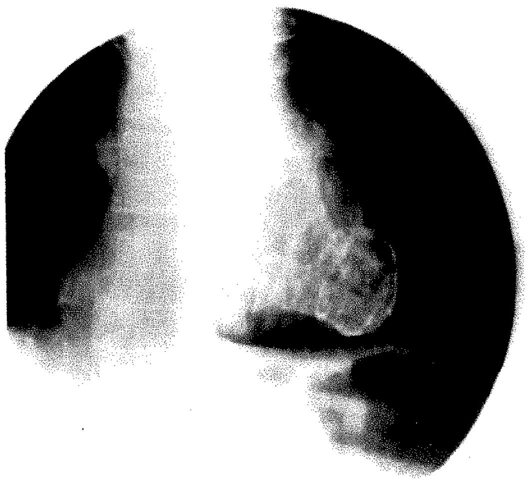

FIG. 3. Overpenetrated spot roentgenogram shows mottled calcification within the calcified "cystic" wall.

scribed 12 times in 8 reports: Scholz;[10] Moore;[9] Atwood *et al.*;[1] Bogoch and Christopherson;[4] Laitinen and Thomander;[7] Lasky;[8] Shapiro *et al.*,[11] 3 cases; and Testelli and Pilz,[12] 2 cases. Although clinical information is not available in all of these reports, this is only the second reported instance of this entity in a woman.[7]

Similar perispherical calcification of the ventricular myocardium had been reported in cases of Echinococcus (hydatid) disease involving the heart.[3,13,15] This diagnosis was considered originally in the present case, but the rarity of the disease, the fact that the patient had never lived, or traveled, in an endemic area, the negative skin and complement fixation tests, and the strong evidence supporting the diagnosis of coronary artery disease and old myocardial infarction, excluded it from consideration. Calcification within the walls of pericardial cysts[14] and in myocardial tumors[2] may rarely resemble this lesion.

SUMMARY

A case of perispherical calcification at the site of an old myocardial infarction is described in a 55 year old woman. Twelve previous similar cases have been reported in the medical literature.

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ROENTGENOGRAPHIC FINDINGS IN CONSTRICTIVE PERICARDITIS*

ANALYSIS OF 21 CASES

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IOWA CITY, IOWA

THE variations in the appearance of the heart and lungs in constrictive pericarditis were described by Heinz and Abrams[4] who emphasized that the heart may be enlarged. The older literature made frequent references to the "small heart" of constrictive pericarditis and not until relatively recently was it appreciated that the size and shape of the cardiopericardial silhouette may vary considerably. These variations are a reflection of the extent and distribution of the constricting pericardial sheets and bands. The constriction may affect the right sided cardiac chambers more than the left, or *vice versa*. Occasionally both ventricles are equally restricted in their diastolic expansion. Residual fluid in the pericardial space may also alter the cardiopericardial contour.

Numerous diseases of the heart may mimic constrictive pericarditis clinically and the diagnosis is frequently difficult. Since the roentgenographic findings may be nonspecific, special procedures such as angiocardiography, roentgen kymography and cineangiocardiography have been utilized. Kymography has fallen into disuse and rapid film angiography is useful only for confirming constriction in the region of the right atrium. Recently a new "diastolic snap sign" has been described in a small number of cases studied by cineangiocardiography.[1] This consists of an abrupt restriction in the diastolic expansion of the ventricles, and is said to be specific for pericardial constriction. The ultimate usefulness of this sign will have to await its demonstration in a larger number of cases and its absence in other types of heart disease.

MATERIAL AND METHODS

During the years 1956 through 1966, 21 cases of constrictive pericarditis were surgically proved and treated at the University of Iowa Hospitals and the Iowa City Veterans Administration Hospital. The records and roentgenograms of these patients have been reviewed and form the basis of this report. Although in most cases a definite etiology could not be established, there were several instances in which a specific inflammatory agent or an episode of trauma to the chest could be implicated as the inciting factor.

The patients ranged from 15 to 70 years of age. There were 17 men and 4 women. All patients had roentgenograms in frontal, lateral and both oblique projections. Fluoroscopy was done in 18. An intracardiac carbon dioxide study was done in 1 patient and angiocardiograms were done in 2. No cineroentgenograms or cineangiograms were obtained. The roentgenograms were examined for the presence of pleural effusion, pulmonary vascular congestion, and pericardial calcification. The cardiothoracic ratio was measured and the cardiac chambers and great vessels were evaluated for the presence or absence of enlargement. In a few cases it was not possible to assess chamber enlargement accurately because of overlying pleural fluid. In these cases the structure in question was listed as not being enlarged. The results of these findings are listed in Table I.

Review of the fluoroscopic reports revealed that cardiac pulsations were decreased in 17 of 18 patients (95 per cent). In the one patient who had an intracardiac carbon dioxide study, the examination was

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Table I

ROENTGENOGRAPHIC FINDINGS IN 21 CASES OF CONSTRICTIVE PERICARDITIS

	Number	Per cent
Pulmonary Abnormalities		
Pulmonary vascular congestion	11	52
Pleural effusion	10	48
Cardiovascular Abnormalities		
Enlarged pulmonary trunk	19	90
Enlarged right ventricle	17	81
Enlarged left atrium	16	76
Enlarged left ventricle	14	67
Pericardial calcification	12	57
Enlarged right atrium	9	43
Enlarged superior vena cava	7	33
Cardiothoracic ratio greater than 0.5	6	25
Enlarged azygos vein	4	19

positive and both patients with angiocardiograms had positive studies.

DISCUSSION

This series of cases again illustrates the previously described variations of the cardiopericardial silhouette in constrictive pericarditis. The incidence of pulmonary vascular congestion and pleural effusion is similar to that reported by Heinz and Abrams[4] who also made a careful analysis of 21 cases. Fluoroscopy in this group of patients was positive in 95 per cent as compared to 66 per cent in their series. This suggests that fluoroscopy is still one of the most useful procedures in the examination of these patients, although it must be kept in mind that normal pulsations may sometimes be seen. Fluoroscopy with image amplification or television monitoring represents a great improvement over the conventional fluoroscope in evaluating pulsations of the various cardiac borders and this may explain in part the greater number of positive findings in this more recent group of patients.

The pulmonary trunk was considered to be enlarged in 90 per cent of this group of patients, which is appreciably more than in previously reported series. Straightening or convexity of the left upper cardiac margin below the aortic knob was interpreted as enlargement of the pulmonary trunk. It is probable that in some of these cases this appearance was caused by pericardial thickening which filled in the usual concavity of this segment of the cardiac border. Regardless of the exact pathologic process, straightening or convexity of the left upper cardiac border appears to be an important finding which has not been previously emphasized.

The right ventricle was thought to be enlarged in 81 per cent of these cases. This does not differ markedly from previously reported series, although it is a slightly high figure. It must be kept in mind that enlargement of the right ventricle is frequently difficult to evaluate, especially in the presence of other chamber enlargement.

This group demonstrated a large left atrium in 76 per cent, which is considerably more than in the series of Heinz and Abrams.[4] However, Spodick[5] makes the statement that left atrial enlargement may occur in up to 80 per cent of cases.

The number of cases interpreted as showing an enlarged left ventricle is also higher than in other series. Here again, a thick

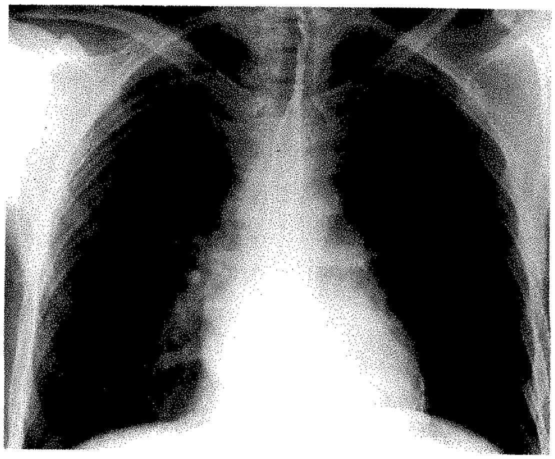

Fig. 1. The superior and inferior venae cavae are enlarged. The left upper cardiac border is convex with partial obscuration of the aortic knob. Calcium is visible at the apex and could be seen both anteriorly and posteriorly in the lateral view.

pericardium may be responsible for posterior protrusion of the cardiac shadow above the diaphragm as well as downward and lateral protrusion in the frontal projection, giving a false impression of left ventricular enlargement.

Pericardial calcification was seen in 12 cases (57 per cent). Although the heaviest deposition of calcium was always located anteriorly, the pericardium adjacent to the diaphragm was frequently calcified also and careful examination of lateral and oblique roentgenograms revealed calcification posteriorly in all but 2 instances.

The right atrium was believed to show enlargement in 43 per cent of the patients and the superior vena cava in 33 per cent. An enlarged azygos vein was seen in 19 per cent. The incidence of these findings does not differ markedly from that in previously reported groups of cases.

One-fourth of our cases demonstrated a cardiothoracic ratio of 0.50 or greater which again points out the fact that cardiomegaly may occur in the presence of constrictive pericarditis.

The one patient in whom a positive carbon dioxide intracardiac study was obtained had an accumulation of very thick exudate in the pericardial space which was causing cardiac constriction.

Two patients had angiocardiograms which were positive by the criteria of Figley and Bagshaw.[3] The thickness of the soft tissue shadow lateral to the inner aspect of the right atrium exceeded 4 millimeters. The lateral margin of the right atrial lumen was straight instead of convex outward and there was no change in the

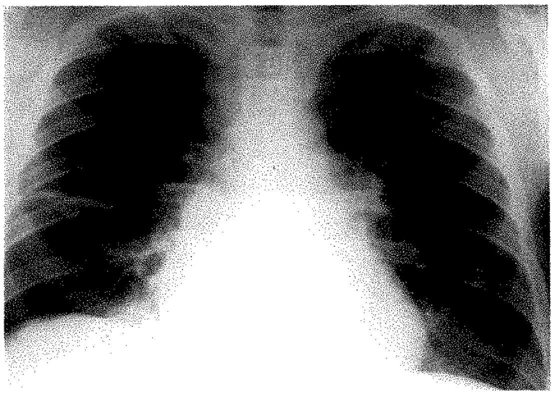

Fig. 3. There is striking dilatation of the superior vena cava and of the azygos vein. Again evident is fullness of the left upper border with complete obliteration of the shadow of the aortic knob. Fluid is present at both bases and in the minor fissure. No pericardial calcification was present in this case.

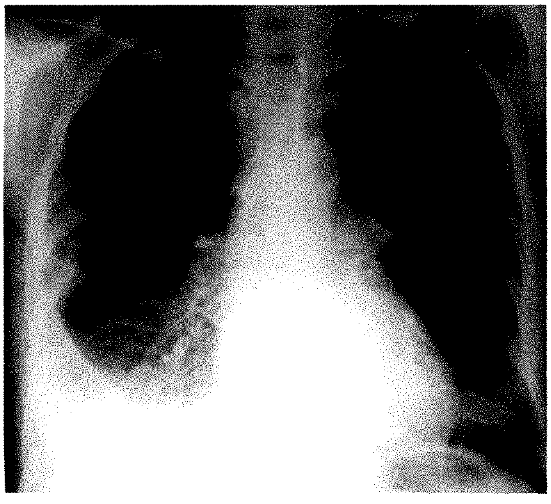

Fig. 2. Although the cardiac configuration is quite different than in Figure 1, there is straightening of the left upper cardiac border. There is a right pleural effusion. Calcium is visible inferiorly and along the left border. Oblique and lateral views revealed it to be present both anteriorly and posteriorly.

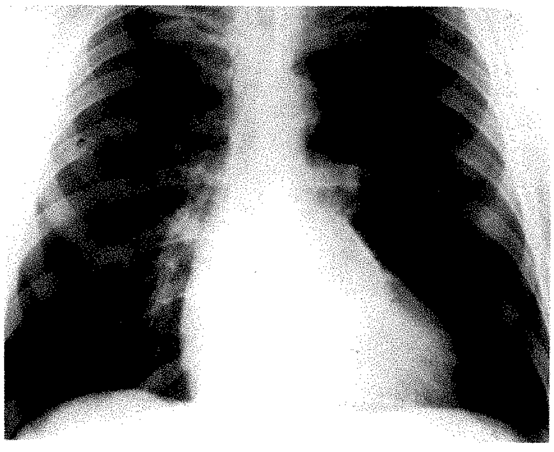

Fig. 4. The heart is enlarged with some prominence of the shadow of the pulmonary trunk and left pulmonary artery. Calcium is seen inferiorly and on the left. Other projections revealed its presence both anteriorly and posteriorly.

configuration of this border throughout the sequence of roentgenograms, indicating rigidity of the wall. The superior vena cava was dilated.

Figures 1 through 4 illustrate some of the features of these cases.

SUMMARY

The roentgenographic findings have been reviewed in 21 cases of proved constrictive pericarditis. Fluoroscopy showed absent or decreased pulsations in 95 per cent and remains an important diagnostic test, particularly with the advent of image amplification and television monitoring. In this series the left upper cardiac border was straight or convex in 90 per cent of patients. This is an important finding which has not been stressed sufficiently. As has been described before, the cardiopericardial silhouette may be enlarged and its configuration may vary considerably. Angiocardiography is generally not required but may be helpful in selected cases.

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ANGIOCARDIOGRAPHY IN DIAGNOSIS OF EFFUSIVE-RESTRICTIVE PERICARDITIS*

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IN A recent review article, Schnabel[10] questions the efficacy of the term "constrictive" used to describe the result of a thickened pericardium impinging on, or adherent to the heart. White[16] and many others as far back as Lower[5] in 1669, and Chevers[2] in 1842, recognized the basic problem to be mechanical. All of the primary and secondary pathophysiologic alterations, symptoms, and signs are secondary to and comprehensible if the mechanical alteration is appreciated. Schnabel points out that the problem is one of restriction of cardiac movement and constriction of the heart; *i.e.*, it is the exception, rather than the rule to find a small heart associated with this disease.

Since the writings of Lower,[5] Chevers,[2] Wilks,[17] Pick,[6] Sauerbruch,[9] Churchill,[3] and White,[16] little has been added to the description or therapy of the disease. Numerous individual case reports have ascribed the etiology of the disease to uncountable stresses, bacteria, fungi, and parasites. However, one aspect of the pathogenesis of the disease has been consistently presumed or disregarded. Recognition of the importance of the pericardial effusion that accompanies the inciting agent is essential to the understanding of the restrictive result that has been called "constrictive pericarditis."

The purpose of this paper is to emphasize the importance of pericardial effusion in the pathogenesis of the syndrome of restrictive pericarditis. Angiocardiographic examination, herein recorded, facilitated the definitive diagnosis of effusion in six representative cases of effusive-restrictive pericarditis.

Effusive-restrictive pericarditis may be defined as the syndrome resulting from pericardial effusion and the scarring that eventuates in restriction. In some cases, long intervals of time elapse between the effusive and the restrictive stages. In others, illustrated by 6 cases described herein, there is a rapid transition or simultaneous occurrence of the effusive and restrictive phases. Diagnosis of either pericardial effusion or restrictive pericarditis is often difficult; the combination of the two is even more so. Because relief of symptoms and cure are possible with pericardiocentesis and pericardiectomy, diagnosis is essential.

Angiocardiography has proven reliable for diagnosis of pericardial effusion.[12,13,15,18] A restrictive component associated with pericardial effusion may be recognized when there is elevation of the venous pressure, prolongation of the circulation time, and when the cardiac chambers are relatively normal in size. These findings may also be present in cardiac tamponade, but can be distinguished from congestive heart failure because the latter is associated with dilated cardiac chambers. Differentiation from restrictive disease of the pericardium can be made by pericardiocentesis. When there is cardiac tamponade, removal of pericardial fluid alleviates venous hypertension, but in effusive-restrictive pericarditis the venous hypertension persists.

MATERIALS AND METHODS

During a 4 year period, 6 patients with effusive-restrictive disease were examined in this center. In addition to the routine clinical, laboratory, and roentgenographic

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examinations, every patient underwent intravenous angiocardiographic studies. Serial Schönander angiocardiograms in biplane, and cineangiocardiographic studies in 3 cases were made. Systemic venous pressures were determined by attaching a manometer to the special needle-stopcock (Robb and Steinberg) cannula. Modified circulation time values were obtained with sodium dehydrocholate, according to the technique previously described.[14] The clinical courses, operative findings, and results, (autopsy findings in 2 patients) are summarized below. In 2 patients (Cases II and III) the data obtained from cardiac catheterization substantiated the diagnosis of restrictive pericarditis.

REPORT OF CASES

CASE I. *Effusive-restrictive pericarditis due to Coxsackie B-4.* A 12½ year old boy was admitted on September 4, 1962, because of abdominal swelling, weight loss, anorexia, fatigue, and periorbital edema of 4 months' duration. Five months before admission, he had fever and substernal chest pain which subsided in 1 month. On physical examination, he was afebrile and appeared to be chronically ill. By percussion the border of his heart was determined to be beyond the left mid axillary line. The heart sounds were distant and muffled and the rate was regular at 120 per minute. The blood pressure was 100/80 mm. Hg. The left lower lung field was dull to percussion and the breath sounds were diminished. The liver edge was 5 cm. below the right costal margin; the abdomen contained fluid.

A tuberculin test (intermediate strength) was negative. The venous pressure at the angle of Louis was 250 mm. saline. The electrocardiogram had changes that were interpreted as right atrial enlargement and there was low voltage over the right ventricle. Chest roentgenograms disclosed an enlarged cardiac silhouette (Fig. 1, *A* and *B*). Intravenous angiocardiography on September 6, 1962, revealed: (1) a large pericardial effusion, measuring 20 mm. to the right of the opacified atrium and 30 mm. beyond the outer opacified wall of the left ventricle; (2) some enlargement of the right atrium and ventricle; and (3) prolonged opacification (circulation time, sodium dehydrocholate, 15.5 seconds) of the cardiovascular structures (Fig. 1, *C*, *D* and *E*). Pericardiocentesis yielded small quantities of blood (hematocrit 29 per cent). A few days later, thoracotomy was performed. The pericardial sac was tense; the thickened parietal pericardium was adherent to the visceral pericardium only over the apex. Approximately 75 ml. of bloody fluid separated the layers of pericardium. The visceral pericardium was also

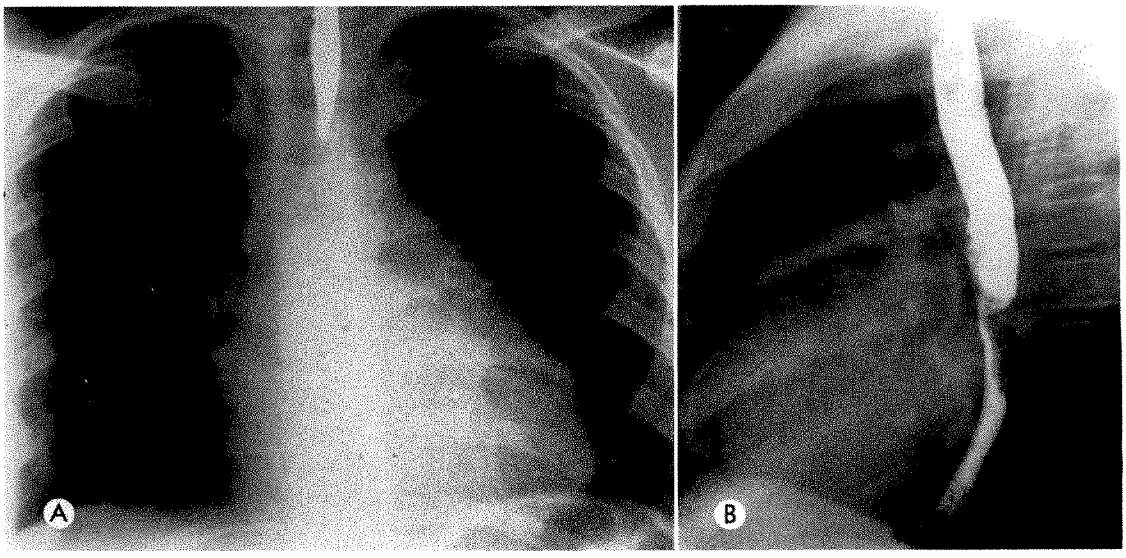
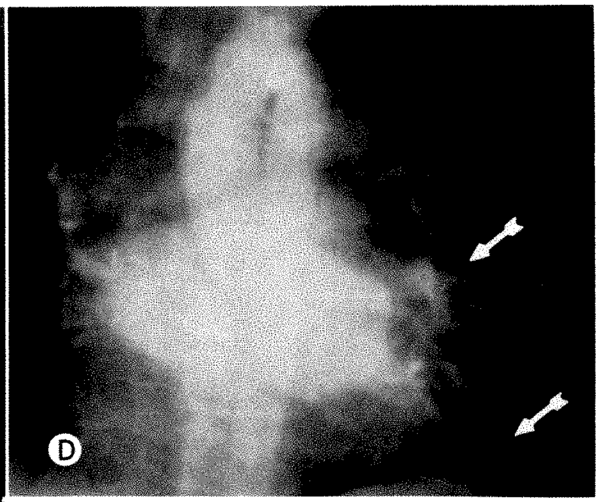


FIG. 1. Case I. (*A*) Frontal teleroentgenogram of the chest showing enlargement of the cardiac silhouette. (*B*) Lateral esophagram showing obliteration of the retrosternal space by the cardiac shadow.



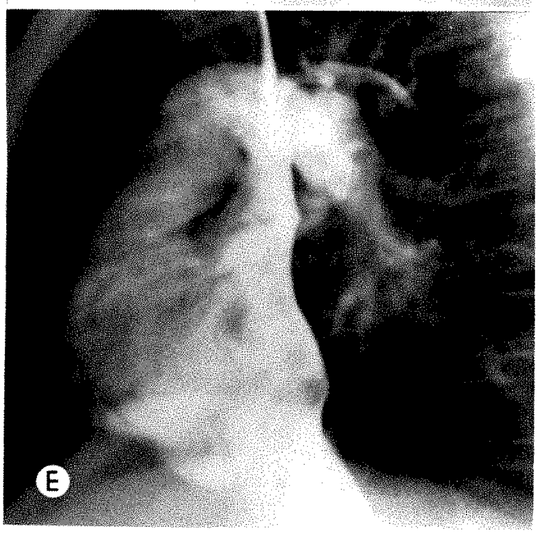


Fig. 1. (*C*) Frontal angiocardiogram showing the dilated superior and inferior venae cavae, the slightly enlarged right atrium, ventricle, and pulmonary artery. Note elevation of the heart above the diaphragm and the soft-tissue density (arrows) adjacent to the opacified right atrial chamber. (*D*) Frontal angiocardiogram showing the enlarged left atrium and pericardial fluid (arrows) beyond the opacified left ventricle. (*E*) Lateral angiocardiogram (biplane view of *C*) showing that pericardial fluid causes displacement of the opacified right heart structures.

thickened and dense (2–3 mm. thick). Visceral and parietal pericardiectomy was performed. During the operation, the myocardium was gray and the heart was noted to have enlarged after the pericardiectomy. The patient tolerated the procedure well with only occasional arrhythmias. Sixteen hours after the operation, cyanosis and shock were evident and the venous pressure was elevated. Cardiac arrest supervened and although resuscitation was successful at first, he died 8 hours later. The final clinical diagnosis was constrictive pericarditis of undetermined etiology. Histologic sections of the excised pericardium contained chronic inflammatory cells scattered throughout loose and dense, richly vascularized fibrous tissue.

The autopsy was performed by Dr. R. Weidenbacker. The pertinent anatomic findings were limited to the heart. Only small remnants of pericardium remained about the inferior vena cava and the pulmonary veins; the surface of the heart was shaggy and hyperemic. The heart was 250 gm. (expected weight 124 gm.); all chambers were dilated to about two

times the normal size. The valve rings were also dilated, but to a less degree. The myocardium was mottled purple, pale, and flabby; the base of the right ventricle was 3 mm. thick, while that of the left was 10 mm. The endocardium of the right and left atria was focally opaque. Focal, subendocardial hemorrhages were present in either ventricle. The coronary arteries were normal. Multiple histologic sections from all areas of the heart were examined. The myocardium was covered by collagenous connective tissue in which there were numerous vascular channels of varying sizes, many containing recent thrombi. Numerous mononuclear cells were scattered throughout the connective tissue and in the outer one-third of the myocardium of all chambers. A layer of fibrin admixed with neutrophils and erythrocytes covered the entire surface. The myocardium was congested; focal hemorrhages were present. Scattered myofibers were hypereosinophilic and others contained clear sarcoplasmic vacuoles. Moderate numbers of perivascular collections of lymphocytes and neutrophils were present in the myocardium of all chambers and septa. Sections from the grossly-described areas of opacified endocardium revealed only focal hypocellular endocardial fibroelastosis.

The lungs, liver, spleen, and kidneys were heavy and congested. Other organs were normal. Coxsackie B-4 virus was cultured from the pericardial fluid obtained at the time of pericardiectomy. No other tissues were examined for the presence of the virus.

Case II. *Effusive-restrictive pericarditis probably due to Histoplasma capsulatum.* A 23 year old woman was admitted on October 9, 1962, with the complaint of chest pain of 3½ weeks' duration which had begun abruptly while she was in the West Indies. She described a "vice-like" left chest pain which increased with inspiration. A roentgenogram of the chest, taken on return to New York City, showed enlargement of the cardiac silhouette.

Physical examination at this hospital revealed a well developed and well nourished woman with slight fever, but no distress. A pleural friction rub was heard over the base of the right lung. A loud to-and-fro pericardial friction rub was heard along the left sternal border. The heart sounds were distant; there were no murmurs and the blood pressure was 100/60 mm. Hg. A roentgenogram of the chest showed a huge cardiac silhouette, bilateral pleural effusion, and calcific deposits at the hilus and mid portion of the left lung (Fig. 2*A*). Pericardiocentesis on October 11, 1962, yielded 10 ml. of turbid yellow fluid. On October 19, 1962, right thoracentesis yielded 250 ml. of turbid yellow fluid. Smears and cultures of these were negative. Venous pressure on November 6, 1962, was 185 mm. saline at the level of the right atrium. First and second strength tuberculin tests were negative. The histoplasmic skin test was positive; complement fixation test for Histoplasma capsulatum was positive to a titer of 1:32. The electrocardiogram showed low amplitude and ST and T wave abnormalities that were interpreted as being consistent with pericarditis. She was improved when discharged on November 7, 1962.

On October 20, 1963, 13 months after onset of symptoms, she was readmitted because of amenorrhea. She had had dyspnea on exertion. There was slight distention of the neck veins, the chest was clear to auscultation and the heart was slightly enlarged by percussion. The blood pressure was 115/80 mm. Hg. The liver was enlarged and the edge was 6 cm. below the right costal margin. There was no peripheral edema. The electrocardiogram showed low amplitude and abnormal T waves. The venous pressure was 170 mm. saline at the level of the angle of Louis. A roentgenogram of the chest showed enlargement of the cardiac silhouette and calcific deposits at the left hilus (Fig. 2, *B* and *C*).

Intravenous angiocardiography on October 23, 1963, showed prolongation of the circulation (sodium dehydrocholate 16 seconds, average normal 8 seconds) and slight enlargement of the left atrium which measured 9.5×7 cm. (average normal 8×5.5 cm.). The pericardium was thickened 10 mm. beyond the right atrium; on the left side it measured 30 mm. (Fig. 2, *D*, *E* and *F*). Right thoracentesis yielded 200 ml. of turbid yellow fluid. Pericardiocentesis on October 23, 1963, yielded no fluid, but on October 31, 1963, 30 ml. of serosanguineous fluid was obtained. Smears and cultures of the pleural and pericardial fluids were negative. Cardiac catheterization by Dr. Daniel S. Lukas on November 1, 1963, revealed high right atrial, ventricular, pulmonary arterial and pulmonary wedge pressures (18, 38/21, 34/23, and 23 mm. Hg, respectively), all of which increased markedly after exercise to 34, 58/37, 54/39, and

44 mm. Hg, respectively. Right ventricular compliance during diastole was present and the high pulmonary venous hypertension was consistent with the diminution of distensibility of the left ventricle. The diagnosis was marked restriction of both ventricles.

Thoracotomy was performed on November 17, 1963. Pulsation of the pericardium was markedly diminished. The pericardium was granular throughout and the parietal pericardium over the right ventricle was 3 mm. thick. Clear, light yellow fluid filled the small pericardial space. Incision of the pericardium over the left ventricle and pulmonary artery did not result in increased contraction of the heart. Accordingly, partial decortication of both ventricles was performed. Although cardiac contractions and excursions were markedly improved, the venous pressure at the conclusion of the operation was 240 mm., compared to the 390 mm. saline at the beginning of anesthesia. She was given digitalis following the operation, but the venous pressure remained elevated (250 mm. saline). Despite transfusion of blood, the blood pressure decreased and the pulse rate increased. She died 24 hours after operation.

The autopsy was performed by Dr. F.Raafat. The thick, gray-white tissue that had been found at the time of surgery, had been mostly removed from the anterior surface of the heart and partially removed from the right, left, and diaphragmatic surfaces. The decorticated cardiac surfaces were shaggy and slightly hyperemic. Fragments of dense, gray-white tissue remained over the right and left ventricles and over most of the right atrium. The pericardial space surrounding the left atrium and the distal portions of the pulmonary veins was totally obliterated. Instead, these structures were surrounded by a mass of inelastic, dense, gray-white tissue, 5–7 mm. thick that blended imperceptibly with the pericardium. Similar tissue surrounded the base of the heart and the root of the aorta. The pericardial reflection around the root of the pulmonary artery formed a circumferential band, 1.0 cm. broad, that constricted the lumen of the main pulmonary artery, beginning a few millimeters distal to the superior margin of the aortic sinuses. Calcific deposits were present in this tissue. A cleavage line was not identified at any point where the pericardium had not been surgically resected. Histologic sections of the pericardium were composed of dense collagen in which there were numerous small blood vessels and scattered mononuclear cells. Granulomas, composed of amorphous material, and foreign body-type giant cells, surrounded by epitheloid cells and lymphocytes, were present in all sections from all areas of the pericardium. Neither tubercle bacilli, nor hyphae, nor spores were identified. Fibrin, admixed with neutrophils and erythrocytes, was present over the decorticated surfaces.

Granulomas, similar to those described above, were identified in the lungs, liver, spleen, and pulmonary hilar lymph nodes. With the use of suitable media and special stains, no microorganism was cultured or observed in any tissue. The liver, spleen, and kidneys were heavy and showed evidence of passive congestion.

CASE III. *Effusive-restrictive pericarditis due to tuberculosis.* A 62 year old retired truck driver was admitted on January 14, 1965, with a nonproductive cough, dyspnea, orthopnea, and weakness of 4 months' duration. A month earlier, he had been in another hospital following the sudden onset of nocturnal paroxysmal dyspnea; a left thoracentesis was performed and having improved, he was discharged on January 10, 1965. After being at home for 3 days, the cough and dyspnea increased and he was admitted to The New York Hospital. Examination revealed a well developed and well nourished man. The pulse was regular at 100 per minute; the respirations were 16 per minute, and the blood pressure was 94/76 mm. Hg. There was dullness and decreased breath sounds over the bases of both lungs; the heart size was judged normal. The liver was not tender, but the edge was 6 cm. below the right costal border.

The roentgenogram of the chest showed enlargement of the cardiac silhouette and effusions at both lung bases (Fig. 3, *A* and *B*). Right thoracentesis yielded 350 ml. of sterile straw-colored fluid. On January 21, 1965, intravenous angiocardiography revealed pericardial effusion. The pericardial layer measured 20 mm. beyond the opacified right border of the right atrium, and on the left, it measured 30 mm. to the left of the opacified left ventricle (Fig. 3, *C*, *D* and *E*). The circulation time (sodium dehydrocholate) was prolonged to 20 seconds, and the venous pressure was elevated to 110 mm. saline at the angle of

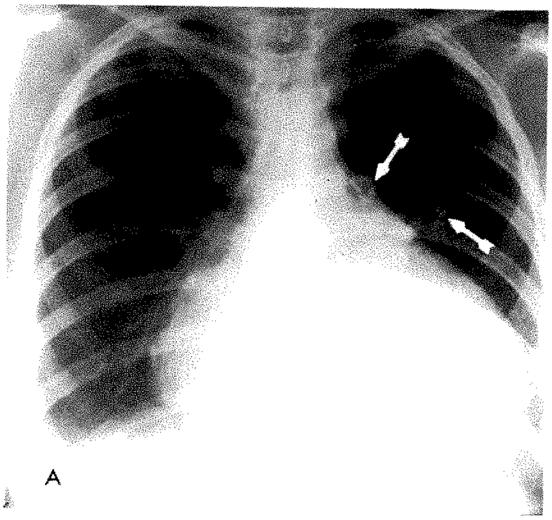


Fig. 2. Case II. (*A*) Frontal teleroentgenogram of the chest showing a huge cardiac silhouette. Note the left hilar and pulmonary calcification (arrows) and bilateral pleural effusion.

Louis. On January 25, 1965, 800 ml. of sterile straw-colored fluid was withdrawn via left thoracentesis. The electrocardiogram showed normal sinus rhythm, rate 100 per minute, and abnormal ST segment and T wave abnormalities.

On February 12, 1965, pericardiectomy was done under general anesthesia. The pericardium was thickened to 1–5 mm. Dense adhesions between the pericardium and myocardium were encountered and required decortication which took 2½ hours. The pericardium was left open at the completion of the operation.

Histologic examination of the pericardium removed at the time of surgery showed that the thickened pericardium was composed of dense collagenous connective tissue with scattered neutrophils and many chronic inflammatory cells. Granulomas were present in all sections. They were constituted of giant cells (both Langhans and foreign body type), lymphocytes, macrophages, and epitheloid cells, all enmeshed in collagen. No foci of coagulative necrosis and acid-fast bacilli were identified. *Mycobacterium tuberculosis* was cultured from the excised tissue. The sputum specimen collected on January 22, 1965, was also found to contain tubercle bacilli 6 weeks later. He improved after treatment with isoniazid and para-aminosalicylic acid, and was discharged on February 28, 1965.

The patient was readmitted on March 22, 1965, because of increasing fatigue and anorexia. He had discontinued the antituberculous drugs because of anorexia. Dullness, decreased breath sounds, and rales were heard over the bases of both lungs. The heart sounds were audible, regular, and without murmurs. The edge of the liver was 6 cm. below the right costal margin. The blood pressure was 120/80 mm. Hg. The venous pressure was 130 mm. saline and the electrocardiogram was normal. Isoniazid and para-aminosalicylic acid were reinstituted. The patient improved, and was dis-

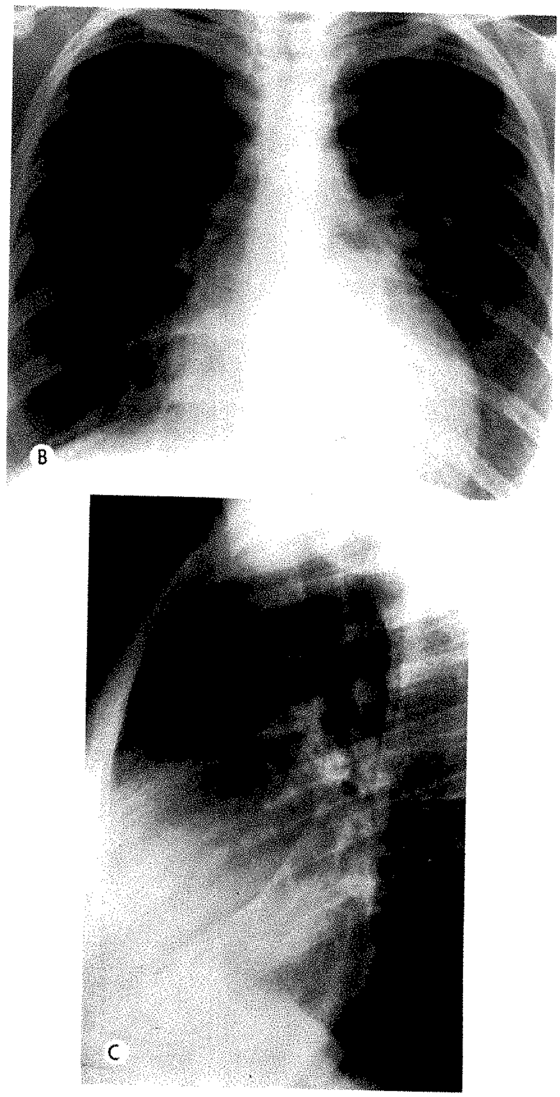


Fig. 2. (*B*) Frontal teleroentgenogram, 13 months later, still showing enlargement of the cardiac silhouette; the pleural effusions have subsided. (*C*) Lateral roentgenogram showing that the cardiac silhouette occupies the retrosternal space.

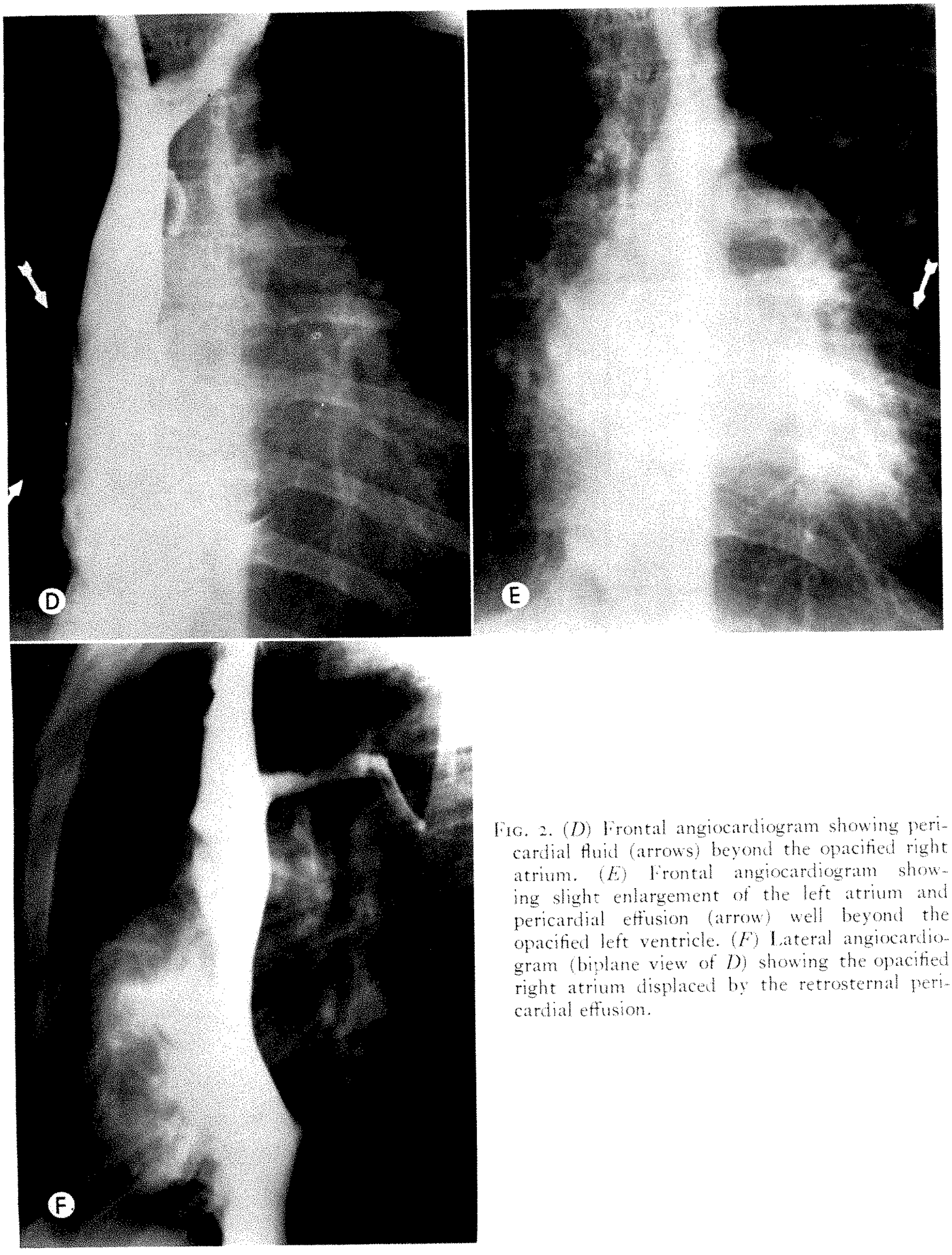


FIG. 2. (*D*) Frontal angiocardiogram showing pericardial fluid (arrows) beyond the opacified right atrium. (*E*) Frontal angiocardiogram showing slight enlargement of the left atrium and pericardial effusion (arrow) well beyond the opacified left ventricle. (*F*) Lateral angiocardiogram (biplane view of *D*) showing the opacified right atrium displaced by the retrosternal pericardial effusion.

charged on May 5, 1965. He was last seen in the pulmonary clinic on May 18, 1966, and was in good health.

CASE IV. *Effusive-restrictive pericarditis due to stab wound.* A 20 year old man was admitted on February 23, 1965, because of dyspnea,

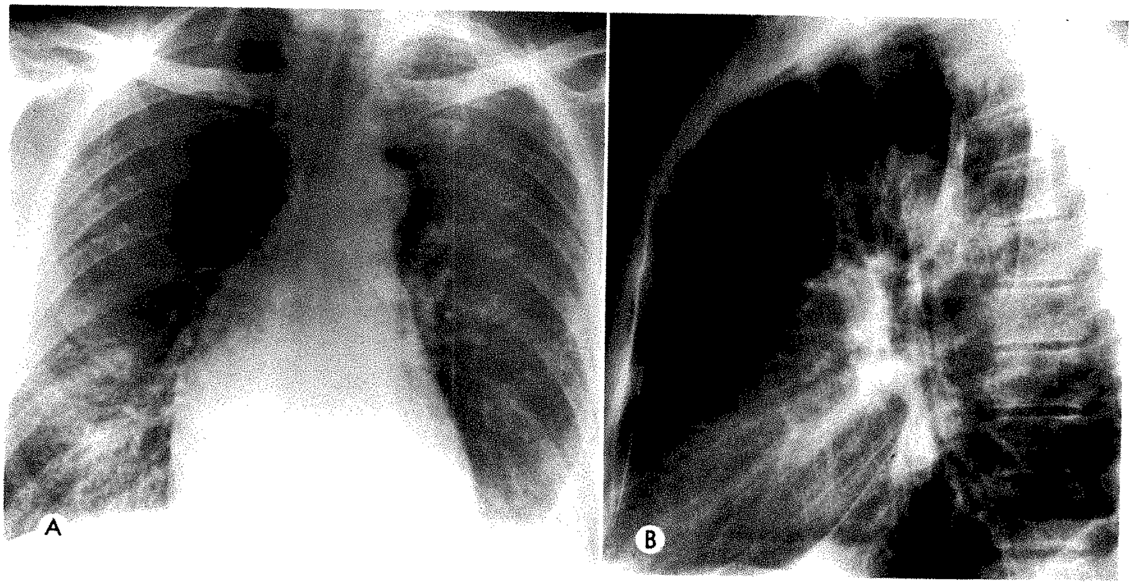


FIG. 3. Case III. (*A*) Frontal teleroentgenogram of the chest showing an enlarged cardiac silhouette and bilateral pleural effusion. (*B*) Lateral roentgenogram showing that the cardiac shadow extends to the sternum.

fatigue, and swelling of the abdomen. On September 11, 1964, he had been stabbed in the epigastrium and was taken to a local hospital. The abdomen was explored, but no damaged structures were found. He required thoracentesis of 50 ml. of blood from the right hemithorax. Ten days later, after apparently recovering satisfactorily, he was discharged. He had no complaints until December 14, 1964, when, at another hospital, a loud pericardial friction rub was heard. He subsequently became dyspneic and sought admission to this hospital.

On physical examination, there was dullness and diminished breath sounds over the base of the right lung. The heart was enlarged to percussion; there were no murmurs, but a pericardial friction rub was heard along the left sternal border. There was a 20 mm. Hg decrease in the systolic blood pressure with inspiration owing to a pulsus paradoxus of 20 mm. The liver was enlarged and the edge was 6 cm. below the right costal margin. Venous pressure was 200 mm. saline at the angle of Louis. Right thoracentesis yielded 70 ml. of sterile cloudy yellow fluid. The electrocardiogram showed normal sinus rhythm, rate 110 per minute, and marked ST segment and T wave abnormalities.

The roentgenogram of the chest showed an enlarged cardiac silhouette and blunting of the right costophrenic sulcus (Fig. 4, *A* and *B*). Intravenous angiocardiograms on February 24, 1965, showed pericardial fluid measuring 10 mm. from the opacified right atrial cavity and 30 mm. from the outer border of the left ventricular cavity (Fig. 4, *C*, *D* and *E*). The circulation time (sodium dehydrocholate) was prolonged to 14 seconds. Pericardiocentesis on March 2, 1965, yielded 50 ml. of sterile serosanguineous fluid. Cardiac catheterization by Dr. Daniel S. Lukas on March 5, 1965, showed restricted filling of both ventricles with marked systemic and pulmonary arterial hypertension. The venous pressure was 200 mm. saline.

Pericardiectomy was performed on April 4, 1965, and disclosed diminished cardiac pulsations. The pericardium was 4–5 mm. thick. Large pieces of parietal pericardium were peeled from the adherent visceral pericardium. At the end of the operation, the venous pressure was 50 mm. saline. Histologic sections of the resected pericardium showed the pericardium to be composed of dense fibrocollagenous tissue in which large numbers of mononuclear cells, foreign body type giant cells and proliferated capillaries were embedded. Hemosiderin-laden macrophages and foci of hemorrhage were scattered throughout. No granulomas or acid-fast bacilli were identified.

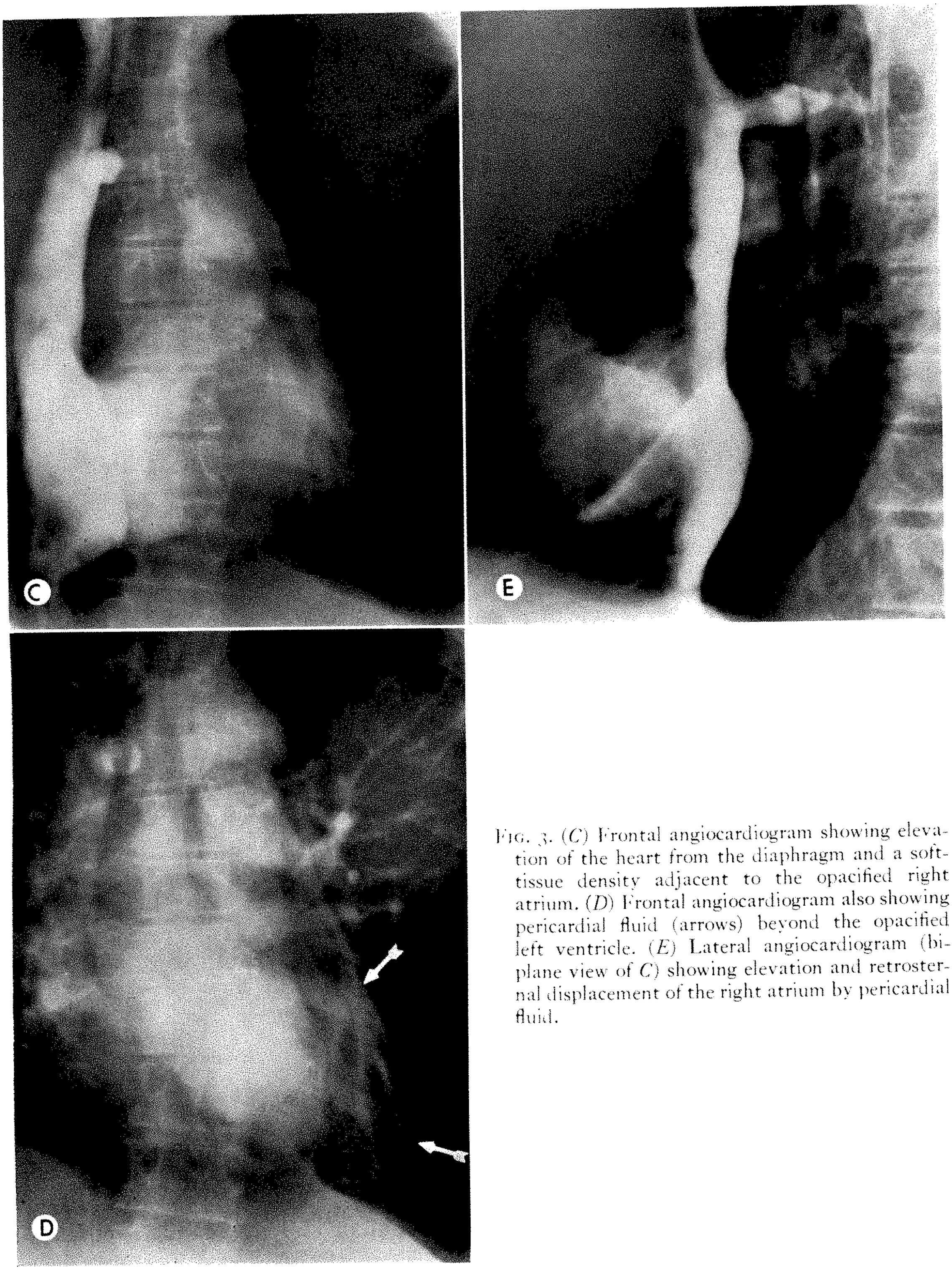


Fig. 3. (*C*) Frontal angiocardiogram showing elevation of the heart from the diaphragm and a soft-tissue density adjacent to the opacified right atrium. (*D*) Frontal angiocardiogram also showing pericardial fluid (arrows) beyond the opacified left ventricle. (*E*) Lateral angiocardiogram (biplane view of *C*) showing elevation and retrosternal displacement of the right atrium by pericardial fluid.

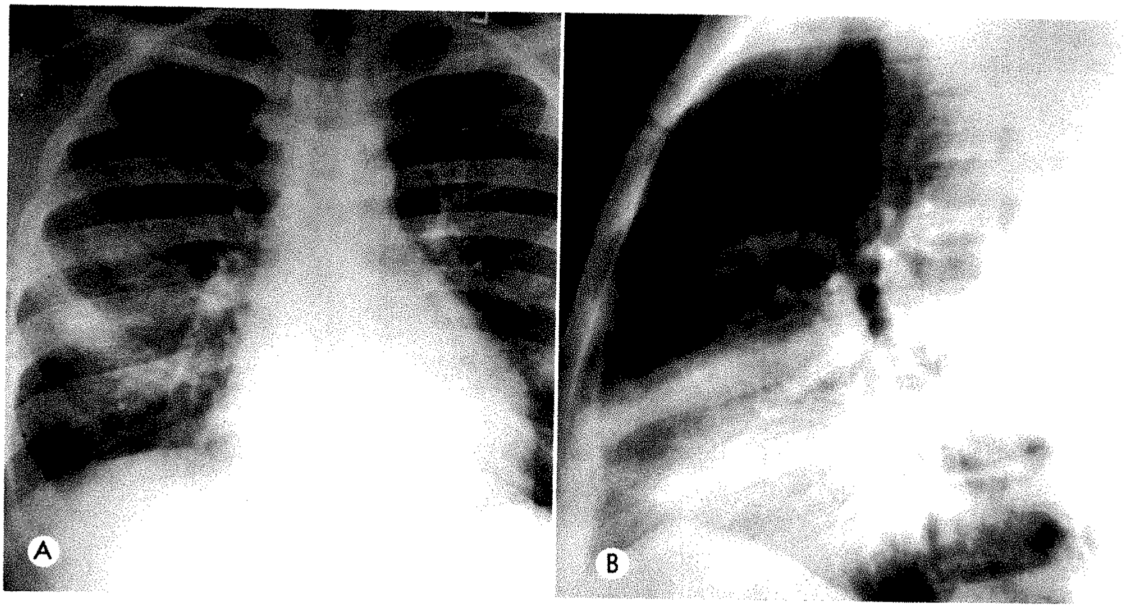
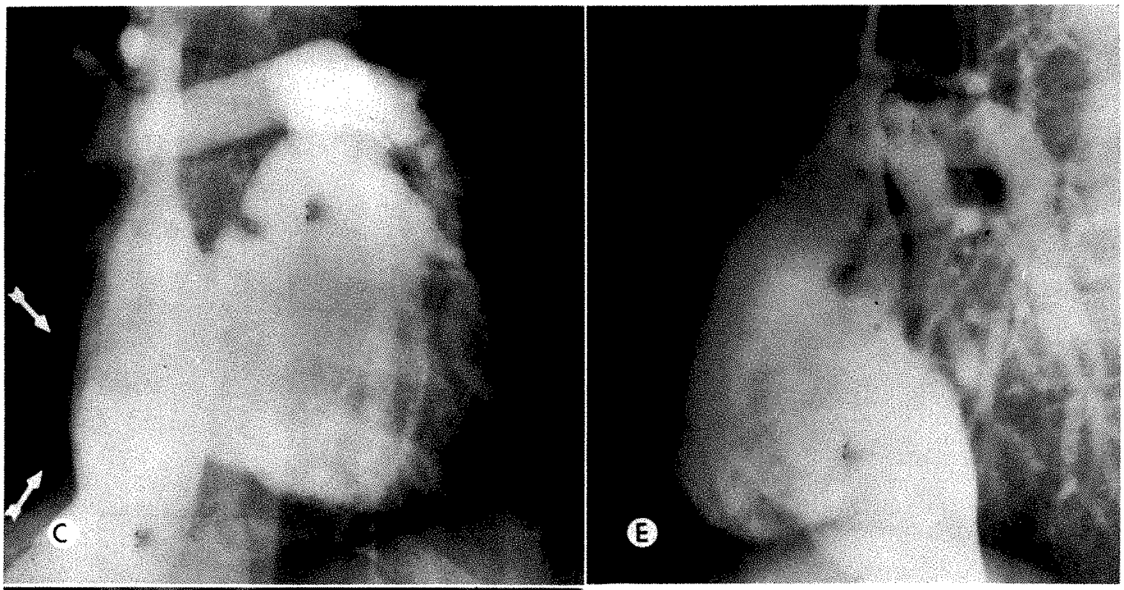


Fig. 4. Case iv. (*A*) Frontal teleroentgenogram showing enlargement of the cardiac silhouette and right pleural effusion. (*B*) Lateral view showing that the cardiac silhouette occupies the retrosternal space.

The patient improved, and was discharged on April 19, 1965. He was well on his last visit to the cardiac clinic on November 5, 1965.

Case v. *Effusive-restrictive pericarditis of unknown etiology.* A 49 year old man was admitted on December 1, 1962, with complaint of abdominal and ankle swelling of 18 months' duration. He had had poliomyelitis at the age of 3 years, but had otherwise been well. On physical examination the heart size was increased beyond the left mid axillary line by percussion; the heart sounds were muffled and distant and there were no murmurs. The rate was 84 per minute and regular, and the blood pressure was 100/82 mm. Hg. The lungs were normal. The liver was enlarged and the edge was 11 cm. below the right costal margin. Both lower extremities and sacrum were edematous. The neck veins were distended and the venous pressure was 275 mm. saline at the angle of Louis. The tuberculin test was positive. The electrocardiogram showed low voltage and ST and T wave abnormalities. The roentgenogram showed a left hydrothorax with enlargement of the cardiac silhouette (Fig. 5*A*). Angiocardiography revealed pericardial effusion measuring 10 mm. to the right of the opacified right atrium and 40 mm. to the left of the opacified left ventricle, and normal cardiac chambers with prolonged opacification time (sodium dehydrocholate) of 26 seconds (Fig. 5, *B* and *C*). Pericardiocentesis yielded 150 ml. of serosanguineous fluid; pericardiectomy was done on December 24, 1962. At operation there was marked thickening of both the visceral and parietal pericardia; the parietal pericardium was 4 mm. thick. There were numerous pericardial adhesions and about 125 ml. of serosanguineous fluid in the pericardial space. There was also marked thickening of the pleura with restriction of the left lung. During the operation electrocardiographic monitoring showed the changes of myocardial fatigue when less than half of the pericardium had been excised. Accordingly, the operation was terminated. The patient's condition improved, and on January 22, 1963, he was re-operated on. At this time the visceral pericardium was removed from the right atrium and ventricle, and the pericardial reflection over the aorta was incised. The left heart pulsations were satisfactory, so further pericardiectomy was not done. The patient improved and was discharged on February 14, 1963. Follow-up examinations, the last one on May 20, 1966, showed the patient to be well; the venous pressure was 85 mm. saline.

Histologic sections of the parietal and visceral pericardia obtained at both operations contained similar lesions. The pericardia were thickened by dense fibrocollagenous tissue that



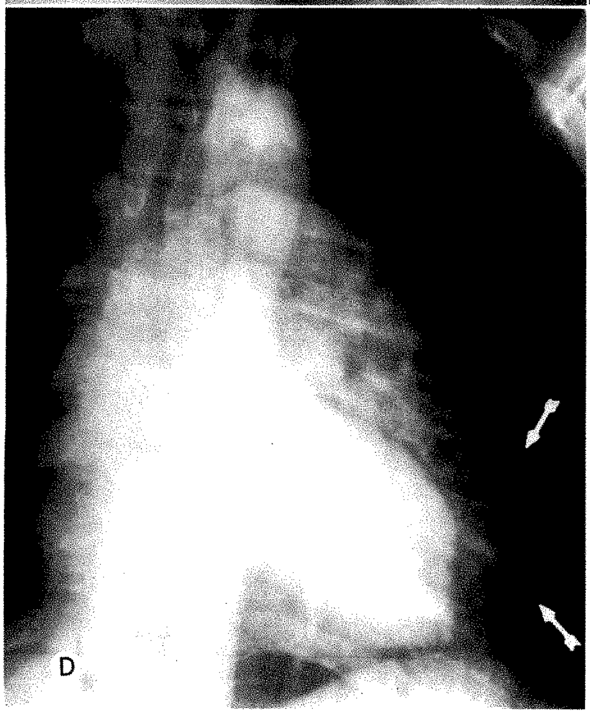


Fig. 4. (*C*) Frontal angiocardiogram showing the thickening along the opacified right atrium (arrows). (*D*) Frontal angiocardiogram showing pericardial effusion (arrows) beyond the opacified left ventricle. (*E*) Lateral angiocardiogram (biplane of *C*) showing retrosternal displacement of the heart by pericardial fluid.

contained numerous scattered lymphocytes and occasional giant cells. No tubercles, granulomas, or microorganisms were identified. Cultures of the excised pericardia were negative.

A biopsied portion of the thickened left parietal pleura was also examined. The pleura was thickened by vascularized fibrocollagenous tissue that contained many mononuclear cells, but no giant cells.

Case vi. *Effusive-restrictive pericarditis of unknown etiology.* A 53 year old man was admitted on February 28, 1963, with complaint of abdominal swelling, fatigue, and dyspnea of 1 month's duration. During that period an electrocardiogram showed nonspecific T wave changes (as compared with a normal tracing 10 months prior to this) and an intermittent pericardial friction rub had been heard. A first

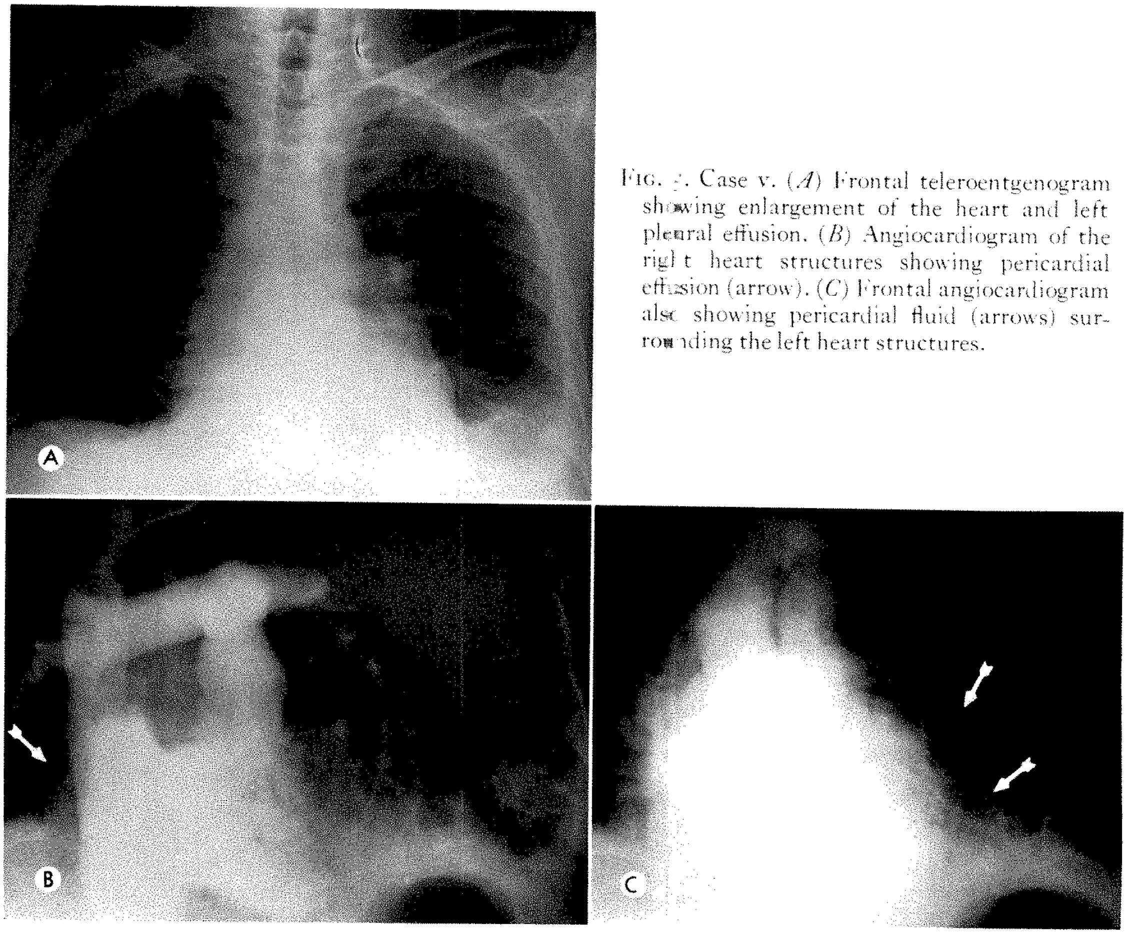


FIG. 6. Case v. (*A*) Frontal teleroentgenogram showing enlargement of the heart and left pleural effusion. (*B*) Angiocardiogram of the right heart structures showing pericardial effusion (arrow). (*C*) Frontal angiocardiogram also showing pericardial fluid (arrows) surrounding the left heart structures.

strength tuberculin test (PPD) was negative, but an intermediate strength test resulted in 2 cm. skin induration. Ten months prior to admission, he had had fever, chills, weakness, and nausea.

Physical examination upon admission disclosed mild respiratory distress, pulse 84 per minute and regular, and blood pressure 120/90 mm. Hg. The left border of the heart was within the midclavicular line and the sounds were distant. The neck veins were distended. The lungs were normal. The liver edge was 4 cm. below the right costal margin; the abdomen was distended and contained fluid. The legs were edematous. The venous pressure was 320 mm. saline at the angle of Louis. The electrocardiogram showed non-specific T wave and ST segment abnormalities. The roentgenogram of the chest showed right pleural effusion (Fig. 6*A*). Angiocardiograms and cineangiocardiograms revealed diminished pulsations. The cardiac chambers were normal in size and were surrounded by pericardial fluid. On the right side the soft tissue density was 20 mm.; on the left, it was 25 mm. (Fig. 6, *B* and *C*). The circulation time (sodium dehydrocholate) was 14 seconds. Pericardiectomy was performed on March 14, 1963. The pericardial sac was tense and 300 ml. of sterile serosanguineous fluid was aspirated from the pericardial space. This resulted in an immediate improvement of the cardiac pulsations. The parietal pericardium was 2–3 mm. thick and both the visceral and parietal pericardium had a granular appearance. The visceral pericardium was removed. The left ventricle and apex were decorticated. Postoperatively the patient did very well and was discharged on March 29, 1963. He was given antituberculous drugs for 6 months. He improved, resumed his regular work, and soon was able to play tennis. He was entirely well when he was last seen in August, 1965.

Histologic examination of the excised visceral and parietal pericardia showed similar changes.

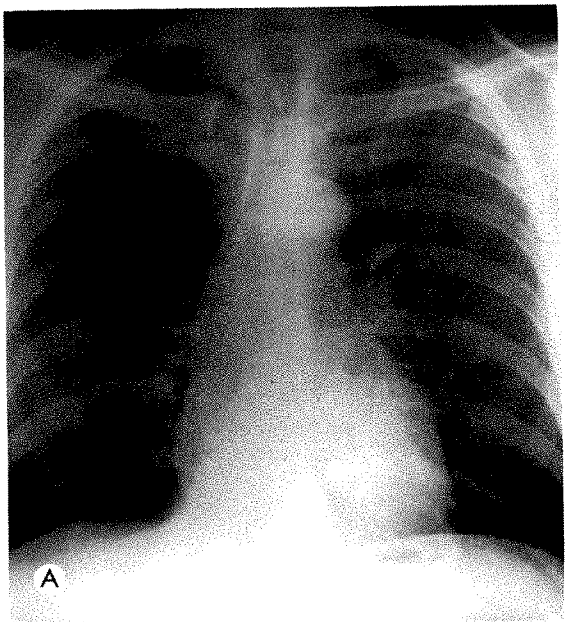
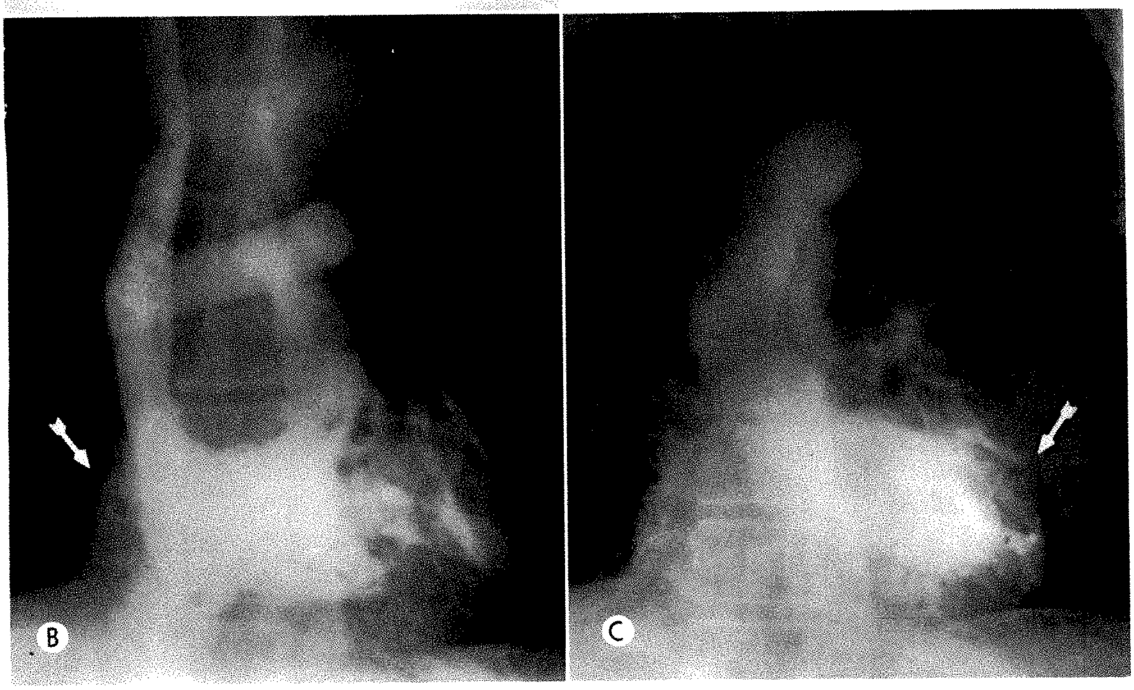


FIG. 6. Case VI. (*A*) Frontal teleroentgenogram of the heart showing a normal sized heart. (*B*) Frontal angiocardiogram showing elevation of the heart above the diaphragm and a widened shadow (arrow) adjacent to the right atrium. (*C*) When the left ventricle is opacified, there is also considerable thickening (arrow) of the outer portion of the left ventricle.



They were both thickened by loose collagenous connective tissue that contained neutrophils and mononuclear cells. Giant cells were scattered throughout the tissue, but no tubercle bacilli, fungi, or bacteria were identified on culture. Dense clusters of lymphocytes were scattered throughout the epicardial fat, especially around blood vessels. The walls of several blood vessels were infiltrated by large numbers of neutrophils that also surrounded these vessels.

RESULTS

The ages of the 6 patients varied from 12 to 62 years, with an average of 36.8 years. Only 1 patient (Case II) was a woman. The etiology of the pericarditis was unknown in only 2 cases, 1 was prob-

Table I

FINDINGS IN EFFUSIVE-RESTRICTIVE PERICARDITIS

Case	Age (yr.)	Sex	Etiology	Venous Pressure (mm. saline)	Modified Circulation Time in Seconds (average normal 8–10 sec.)	Angiocardiographic Size of Pericardial Shadow at	
						Right Atrium (mm.)*	Left Ventricle (mm.)†
I	$12\frac{1}{2}$	M	Coxsackie B-4	250	15.5	20	30
II	23	F	Histoplasmosis?	185	16.0	10	30
III	62	M	Tuberculosis	110	20.0	20	30
IV	20	M	Stab wound	200	14.0	10	30
V	49	M	Unknown	275	26.0	10	40
VI	53	M	Unknown	320	14.0	20	25

* Average normal 2–3 mm.
† Average normal 8–10 mm.

ably caused by *Histoplasma capsulatum*, the other 3 were due to Coxsackie B-4 virus, *Mycobacterium tuberculosis*, and a stab wound. Each patient had enlargement of the cardiac silhouette and liver, pleural effusions, and venous hypertension. The diagnosis of effusive-restrictive pericarditis was established by demonstrating a soft-tissue density surrounding the heart, prolonged circulation time, venous hypertension, and normal, or relatively normal sized cardiac chambers (Table I). Pericardiocentesis yielded fluid in each instance, and in some cases fluid was found at the time of pericardiectomy.

DISCUSSION

Conventional roentgenography, by showing an unusual contour and enlargement of the cardiac silhouette, may provide significant clues for diagnosis of pericardial effusion (Fig. 1*A*; and 2, *A* and *B*). When the retrosternal space is obscured in lateral views (Fig. 1*B*; 2*C*; 3*B*; and 4*B*) and congenital and acquired rheumatic heart has been excluded, the diagnosis of pericardial effusion should come to mind.[15] When there are calcifications in the heart, especially over the region of the ventricles, restrictive pericarditis should be suspected.[12] None of the patients described above, however, had calcifications. This was probably due to the rather short duration of the transition period from pericardial effusion to restriction.[8]

Angiocardiography, by showing a soft-tissue density adjacent to the cardiac borders (in frontal view) can establish the diagnosis of pericardial effusion.[12,13,15,18] The width of the surrounding soft-tissue density is often related to the volume of the pericardial effusion, and pericardiocentesis substantiates the diagnosis. In rare instances, pericardiocentesis does not yield fluid, but this should not be a reason for abandoning the diagnosis of pericardial effusion. This is exemplified by a recent case,[13] in which pericardial fluid was not secured over a 3 year period by pericardiocentesis. This was followed by creation of a pericardial left pleural window following pericardiocentesis which drained the pericardial effusion.

If, in addition to pericardial effusion, the venous pressure is elevated and the circulation time is prolonged, cardiac tamponade or effusive-restrictive pericarditis should be suspected. Venous hypertension and prolonged circulation time also occur in heart failure, but in these cases, the cardiac chambers are dilated.[7,11,12] Finally, despite the fact that pericardiocentesis alleviates the cardiac restriction in effusive-restrictive pericarditis, the venous pressure remains elevated.

Continued elevation of the venous pressure in restrictive pericarditis has long been known.[4] The arm to tongue circulation time is normal in pericardial effusion, but is prolonged in restrictive pericarditis.[1] An-

giocardiography further refines the evaluation of the circulation time by showing the size and prolongation of the contrast material in the cardiac chambers. When there is pericardial effusion alone, the heart is usually normal in size.

SUMMARY AND CONCLUSIONS

Angiocardiography is a reliable method for diagnosis of pericardial effusion and also provides significant data regarding the cardiovascular structures. In frontal view, it shows the classic soft-tissue density of pericardial fluid surrounding the heart; in lateral view, there is retrosternal accumulation of pericardial fluid; and in both positions, there is often elevation of the heart above the diaphragm by pericardial fluid. When venous hypertension, prolongation of the circulation (opacification) time, and relatively normal-sized cardiac chambers coexist with the pericardial effusion, effusive-restrictive pericarditis or pericardial effusion with cardiac tamponade should be suspected. Cardiac tamponade can be ruled out by pericardiocenteses, with alleviation of the venous hypertension. The absence of cardiac dilatation, a common cause of venous hypertension and prolonged circulation time, can be appreciated after scrutiny of the angiocardiograms.

The clinical, surgical, and pathologic features of effusive-restrictive pericarditis are described in 6 patients with the syndrome. Early diagnosis of effusive-restrictive pericarditis can be life-saving, and for this angiocardiography is recommended.

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Dr. Jerimiah A. Barondess kindly gave permission to include Case II in this report.

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A COMPARISON OF VENOUS ANGIOGRAPHY AND RADIOISOTOPE HEART SCANNING IN THE DIAGNOSIS OF PERICARDIAL EFFUSION*

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PERICARDIAL effusion is an important clinical entity requiring prompt diagnosis. The limitations of clinical examinations, electrocardiography, plain film roentgenography and conventional fluoroscopy are well known. The application of angiocardiography with radiopaque contrast medium to pericardial effusion and cardiac dilatation was first emphasized by Dotter and Steinberg in 1951.[4] In 1957, Figley and Bagshaw[6] discussed angiographic aspects of constrictive pericarditis and established criteria important in the differential diagnosis of pericardial thickening and effusion. Durant *et al.*,[5] in the same year, introduced a new method specifically for studying pericardial disease by outlining the lateral border of the right atrium with intracardiac carbon dioxide. In the following year, Rejali and co-workers[9] introduced a method of scanning the cardiac blood pool to determine the presence of pericardial effusion. More recently, radiopaque venous angiography has been re-emphasized in the diagnosis of pericardial effusion.[10] Numerous articles revising the various methods mentioned have appeared in the literature, but studies comparing the different techniques have been infrequent.

MATERIAL AND METHOD

The following study consists of 30 examinations in 25 patients suspected of having pericardial effusion. Examinations consisted of venous angiography utilizing carbon dioxide and radiopaque contrast material, and correlative cardiac photoscanning.

Scout roentgenograms of the chest were made in the upright and left lateral decubitus position utilizing the "over-penetrated" technique. The decubitus examinations were obtained with the patient lying on a stretcher against an upright Bucky diaphragm.

Subsequently, with the patient in a left lateral decubitus position, a No. 16 gauge needle was inserted into an antecubital vein and connected to a tank of pure carbon dioxide by a 3-way stopcock. A 100 cc. syringe was attached to the stopcock and repeatedly flushed with carbon dioxide. Then 75–100 cc. of carbon dioxide were rapidly hand-injected and two 14×17 inch films were exposed sequentially at a 72 inch target-film distance. The patient was maintained in the left lateral decubitus position for at least 5 minutes, then turned into the right lateral decubitus position. Fifty cubic centimeters of 50 per cent hypaque were injected rapidly by hand and two more 14×17 inch films were sequentially exposed.

With either technique, a convex band of soft tissue is visualized between the contrast-delineated right atrial cavity and the surrounding lung tissues. This band (hereafter called "wall thickness") represents the combined thickness of the pleura, pericardium and right atrial wall, and measures 4 mm. or less in the normal adult (Fig. 1, *A* and *B*). With pericardial effusion this convex soft tissue band is increased in width. Generally accepted criteria in the literature[6,10,12] are that a wall thickness of 5–10 mm. is equivocal and may represent pericardial fluid and/or thickening. Thicknesses of 10 mm. or more are thought to be

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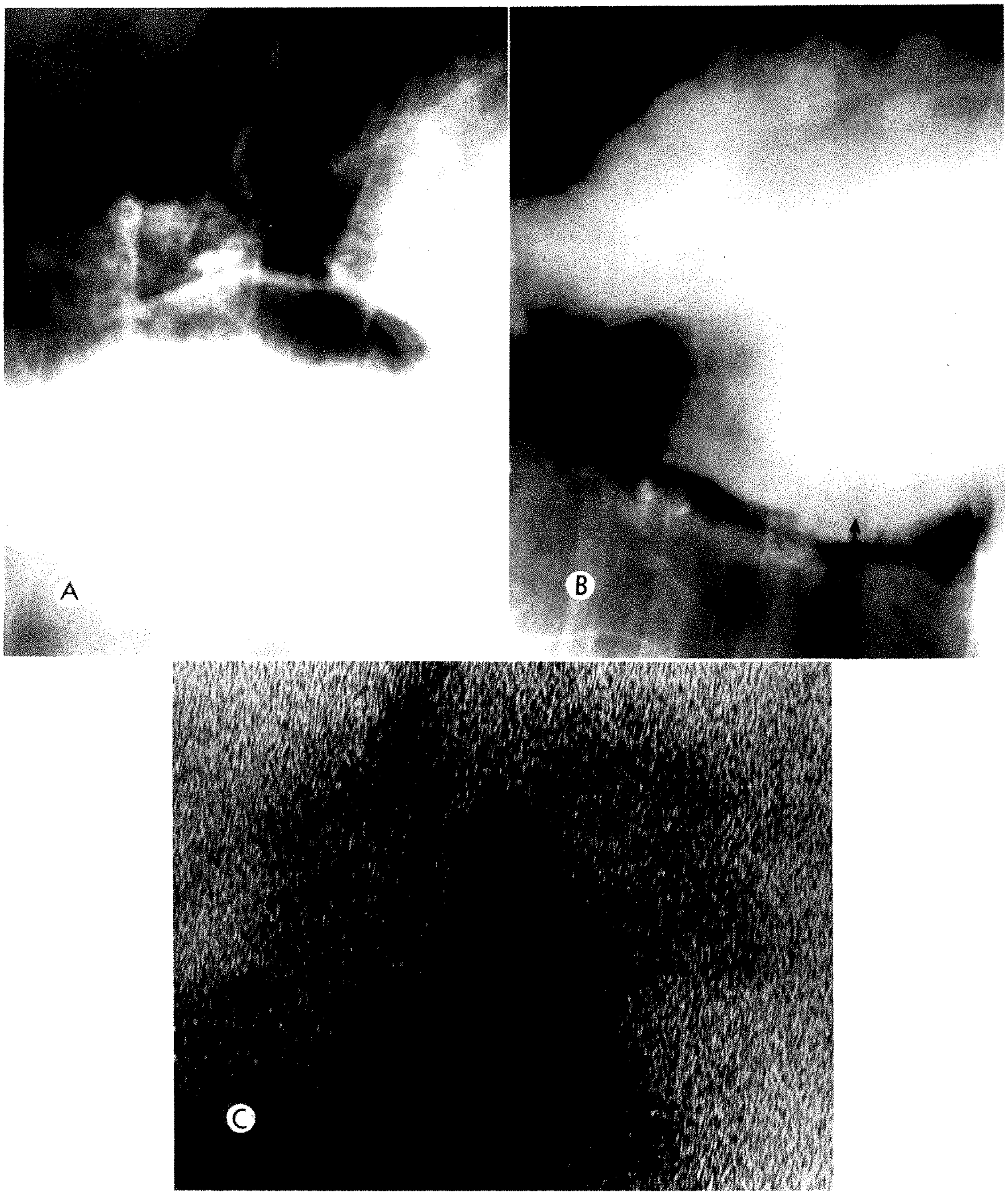

Fig. 1. Normal study. (*A*) Radiolucent shadow of CO_2 in right atrial cavity with normal wall thickness. (*B*) Radiopaque contrast material in right atrial cavity with normal wall thickness (arrow). The normal wall often is difficult to visualize. (*C*) Normal cardiac photoscan.

pericardial effusion. Initially these criteria were applied in this study, but later, the criteria for diagnosis of equivocal effusions were modified.

Following angiography the patients underwent cardiac photoscanning. They were given 2 or 4 mc of technetium 99m-labeled human serum albumin intravenously, prepared by the method of Stern, Zolle and McAfee.[13] Five to 10 minutes later, the pa-

Table I

DISTRIBUTION OF RESULTS OF COMPARATIVE EXAMINATION

No. of Patients	CO_2 Angiography	Radiopaque Angiography	Cardiac Photoscan	Fluid Proven by Pericardiocentesis, Serial Angiography or Autopsy		
				Yes	No	Not Done
8	Normal	Normal	Normal			8
3	Normal	Equivocal	Normal	3		
1	Normal	Positive	Normal			1
1	Equivocal	Equivocal	Normal		1	
9	Positive	Positive	Normal	5		4
3	Positive	Positive	Positive	1	1	1

tients were scanned from the front while lying supine. Ordinarily, a 5×2 inch crystal scanner with a 35 kev. window and a 135 kev. baseline energy setting was used in conjunction with a 43 hole focusing collimator having a 3 inch focal depth and a 0.375 inch radius of resolution at the focal point. The average scanning speed was 50 inches per minute. In some cases an 8×2 inch sodium iodide crystal scanner with a 253 hole focusing collimator having a 3.5 inch focal depth and a 0.375 inch radius of resolution was utilized.[7] The photoscans were interpreted as negative or positive for pericardial effusion on the basis of criteria established by Wagner *et al.*[14] These include comparison of the isotope delimited cardiac blood pool to the transverse cardiac ratio noted on the chest roentgenogram, separation of cardiac and pulmonary blood pool by a zone of decreased radioactivity, and separation of the cardiac and hepatic blood pools.

RESULTS

Thirty examinations were performed on 25 patients. Of these, 17 patients were thought to have abnormal carbon dioxide and/or radiopaque angiography suggestive of pericardial effusion. The distribution of results is noted in Table I.

The wall thickness values obtained for the carbon dioxide and radiopaque angiography agreed within ±2 mm. in 17 of the 25 cases. In the other 8 cases the wall thicknesses recorded by the two methods differed by 5 to 9 mm. In every one of these 8 cases, the wall thickness was greater with positive contrast angiography.

Of 13 cases with unequivocally positive angiography, 10 were found to have normal photoscans (Fig. 2, *A–D*). In 5 of the 10 cases with normal photoscans, pericardial effusion was proved by serial follow-up angiographic studies and/or surgical exploration. These cases are summarized in Table II. In the other 5 cases, no angiographic follow-up studies were obtained. However, these latter cases all showed clinical improvement with decrease in cardiac size and venous pressure.

Three cases were found to have positive angiography and a positive cardiac photoscan (Fig. 3, *A*, *B* and *C*). In 1 case, the "wall thickness" measured 25 mm. by the CO_2 method and 32 mm. with radiopaque contrast material. At pericardiocentesis, 600 cc. of serosanguineous fluid was removed. The patient expired several days later and was noted at autopsy to have a minimal residual pericardial effusion. The second case had a "wall thickness" measuring 24 mm. by the CO_2 method and 32 mm. with hypaque angiography. Pericardiocentesis produced no fluid, but this does not preclude the presence of effusion since this procedure may be quite inaccurate as a diagnostic measure.[11] The third

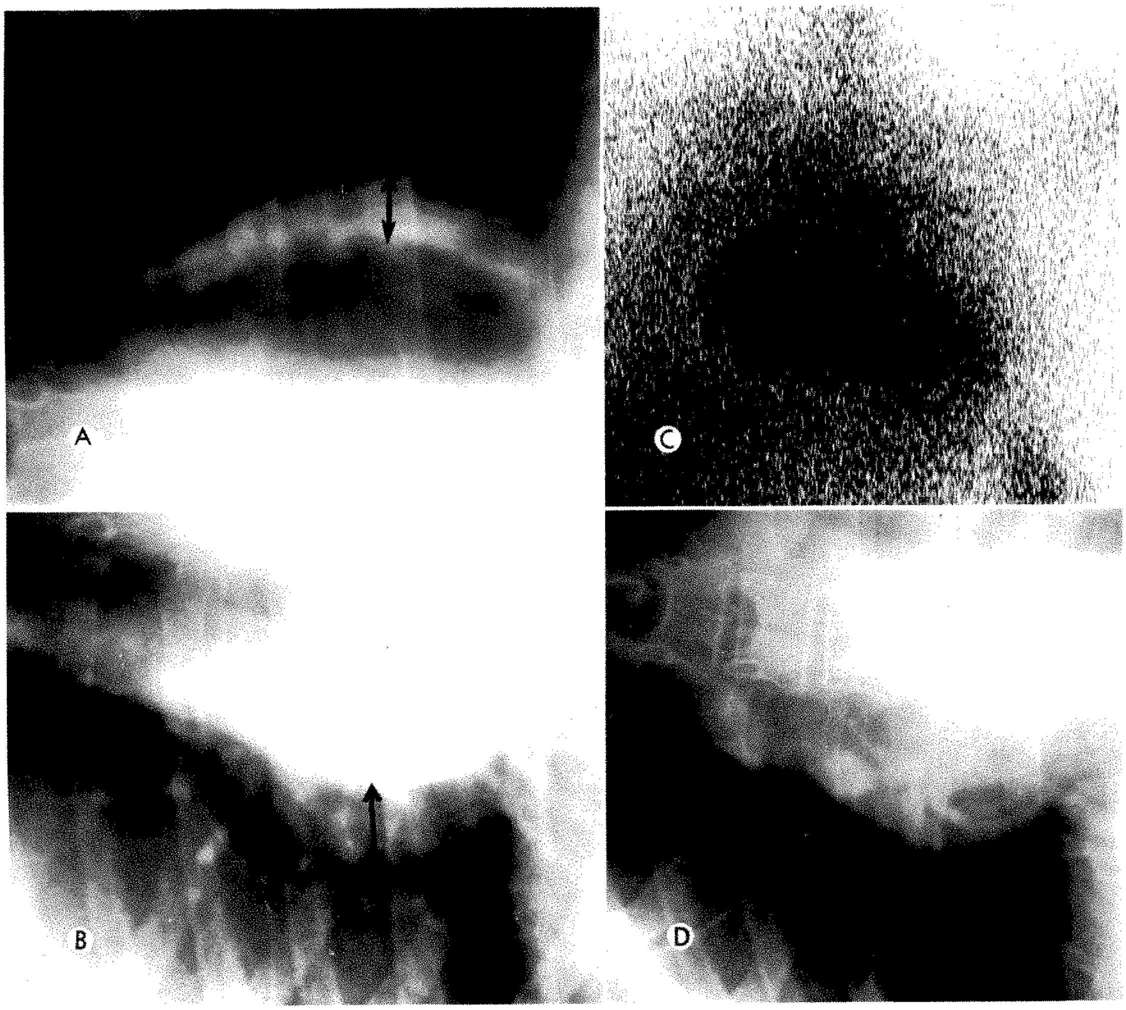

FIG. 2. Positive angiography and normal cardiac photoscan. (*A*) Positive CO_2 study with wall thickness of 15 mm. (arrow). (*B*) Positive radiopaque contrast material study with wall thickness of 21 mm. (arrow). (*C*) Normal photoscan. (*D*) Follow-up normal radiopaque angiography after 6 weeks of clinical therapy.

patient had no follow-up studies at this institution.

DISCUSSION

The normal pericardial sac contains 15 to 30 cc. of fluid.[12] Clinical and experimental studies have shown that pericardial fluid accumulates first in the dependent portion of the pericardial sac.[12] Mellins *et al.*[8] in dog experiments demonstrated that little fluid accumulates in the posterosuperior portions of the pericardium, because pericardial reflections there prevent distention of the pericardial sac. These authors noted that the location of the effusion was not altered to any appreciable degree by a change in the position of the animal.

Studies of Shuford *et al.*[10] indicate that in pericardial effusion in man, considerable fluid shifts take place with a change in the position of the patient. In the majority of their patients with effusion, sufficient fluid remained above the right atrium to render the carbon dioxide method accurate. In two of their cases, however, pericardial fluid shift resulted in a negative or equivocal carbon dioxide study. A single case in the present series had a normal carbon

Table II

FOLLOW-UP IN 5 CASES WITH UNEQUIVOCALLY POSITIVE RADIOPAQUE ANGIOGRAPHY AND NORMAL PHOTOSCANS

Patients	Wall Thickness (mm.) CO_2 Angiography	Wall Thickness (mm.) Radiopaque Angiography	Cardiac Photoscan
11 year old white male with clinical picture of rheumatic fever including congestive heart failure. Decreased voltage on electrocardiography	10	13	Normal
Follow-up—Repeat angiography in 4 weeks. Marked clinical improvement with decreased heart size and normal voltage on electrocardiography		1–2	
49 year old white female with congestive heart failure (R), pleural effusion and cardiomegaly	13	14	Normal
Follow-up—Repeat angiography in 3 weeks. Marked clinical improvement		2	
16 year old Negro female with rheumatic mitral disease. Cardiomegaly	15	20	Normal
Follow-up—Repeat angiography in 6 weeks after bed rest and diuretics. Marked clinical improvement. No pericardial fluid at cardiac surgery		2	
64 year old Negro female with rheumatic mitral disease. Cardiomegaly, fever, pericardial rub	10	19	Normal
Follow-up—Repeat angiography in 6 days showed decreasing fluid. Fibrinous pericarditis and minimal pericardial effusion at autopsy		10	Not evaluated Pleural effusion
55 year old white female with diabetes and congestive heart failure	29	30	Equivocal
Follow-up—Repeat angiography in $3\frac{1}{2}$ weeks showed decreasing fluid. Clinical improvement on bed rest and diuretics		10	Normal

dioxide study and positive hypaque study. Consequently, a negative carbon dioxide study should not discount a diagnosis of pericardial effusion and a radiopaque study should be done in such cases.

Recent experiments with dogs by Adams *et al.*[1] have shown that the amount of CO_2 in the right atrium may have sufficient buoyancy to produce a flotation effect upon the heart suspended within a fluid-filled pericardial sac. This may explain the disparity in wall thickness observed in some of our cases when carbon dioxide and positive contrast medium studies were compared.

In the present series, 3 patients with a normal carbon dioxide study had equivocal hypaque studies (wall thickness of 7, 8 and 10 mm.). At surgery, these patients were found to have 90 to 120 cc. of pericardial fluid. One patient with equivocal carbon dioxide and hypaque studies had a thickened atrial wall at surgery and a normal volume of pericardial fluid.

Therefore, it is suggested that the combination of normal carbon dioxide study and equivocal hypaque study may indicate a volume of pericardial fluid in the range of 100 cc. or less. When both carbon dioxide and hypaque studies measure in this

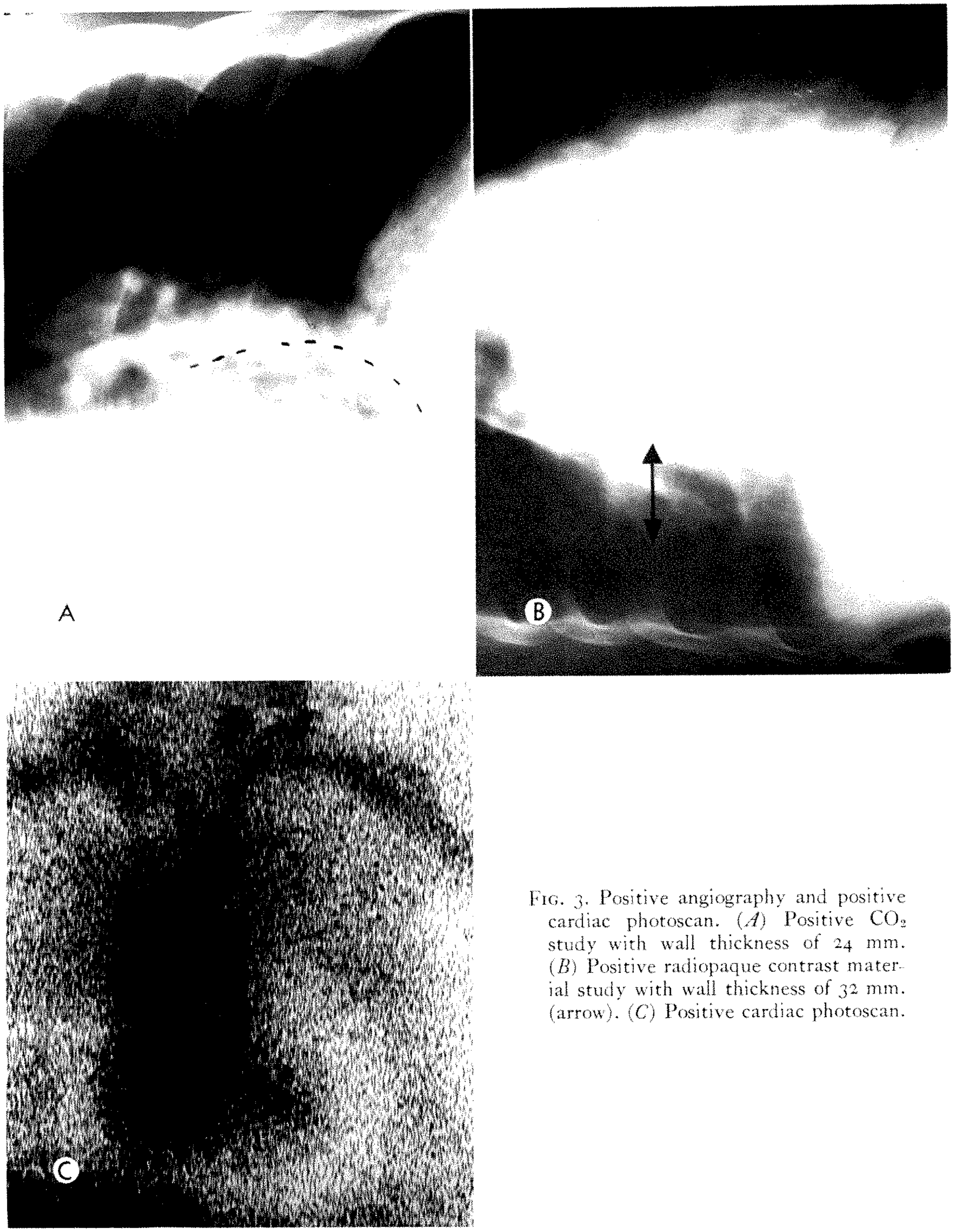

Fig. 3. Positive angiography and positive cardiac photoscan. (*A*) Positive CO_2 study with wall thickness of 24 mm. (*B*) Positive radiopaque contrast material study with wall thickness of 32 mm. (arrow). (*C*) Positive cardiac photoscan.

equivocal range, either a thickened atrial wall, pericardial tumor, or effusion is indicated.

The threshold volume of pericardial effusion, which may be detected by radioisotope scanning, was investigated by

Bonte[2] in 1962, utilizing a phantom consisting of readily distensible rubber balloons placed one inside the other. A radioactive solution was placed in the inner bag and arbitrary amounts of water were placed in the outer bag to simulate a pericardial effusion. The phantom was then submerged within a tank containing radioisotope content comparable to that which would be present surrounding the heart in the natural state. One of the conclusions was "with the experimental apparatus described above, we have easily been able to find experimental pericardial effusions of 300 ml. and above, and have been able . . . to demonstrate effusions in the order of 200 ml." Charkes and Sklaroff,[3] in 1963, studied 13 patients with pericardial effusion of 200 cc. or greater. The authors stated, "It is apparent that the techniques may not be reliable when cardiac enlargement co-exists unless more than 300 cc. of fluid is present."

No comparison of venous angiography with pericardial photoscanning could be found in the literature. In the present series, 10 cases with positive carbon dioxide and radiopaque angiograms for pericardial effusion had normal cardiac photoscans. Five of these cases had proven pericardial effusion. It is suggested that venous angiography may be a more sensitive and reliable test for pericardial effusion in the critical ranges of 200 to 300 cc. It is with this volume of fluid that cardiac tamponade may occur.

SUMMARY

1. In humans, there appears to be a shift of pericardial fluid with shift in position. In the majority of cases, sufficient fluid is retained above the right atrium to render the carbon dioxide method accurate in evaluating effusion. However, in some cases fluid shift may result in a normal or equivocal carbon dioxide study.

2. Because of this pericardial fluid shift, a re-evaluation of these cases now called "equivocal" may be possible. Those with normal wall thickness on carbon dioxide angiography and equivocal wall thickness (5–10 mm.) on radiopaque angiography may indicate free effusion in the range of 100 cc. Those cases with equivocal wall thickness by both carbon dioxide and radiopaque angiography may represent atrial wall thickening, pericardial tumor or pericardial effusion. No clear differentiation can be made in the latter cases.

3. Venous angiography is a more sensitive and reliable test than cardiac photoscanning for pericardial effusion in the critical range of 200 to 300 cc. of fluid.

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A NEW APPROACH TO PULMONARY ANGIOGRAPHY*

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THE conventional approach to pulmonary angiography has been by venous cutdown using the basilic antecubital vein. The percutaneous Seldinger technique,[4] which was developed for arterial catheterization, can be applied to venous catheterization. The percutaneous technique has several advantages, including the speed with which it can be performed, a lesser chance of infection, avoidance of direct manipulation of the vessel, and avoidance of sacrifice of the vein. The purpose of this report is to describe the advantages and technique of performing pulmonary angiography via the percutaneous internal jugular vein approach.

Unfortunately, the percutaneous method cannot be applied consistently to the antecubital vein due to its variability in depth and location. In the use of the standard cutdown technique, the left antecubital vein is preferred since one large continuous curve can be used to pass through the inferior vena cava, right atrium, right ventricle, and pulmonary artery (Fig. 1*A*). The approach from the right arm requires a double curve in the catheter to reach the pulmonary artery (Fig. 1*B*). The femoral approach (Fig. 1*C*) is undesirable in the study of pulmonary thromboembolism. The right jugular approach is the most direct approach requiring a simple single curve (Fig. 1*D*).

Optimal visualization of small vessels is essential if emboli are to be seen so that selective right and left pulmonary artery injections are frequently required. The ease with which the selective positioning of the catheter can be performed and the speed in which the procedure can be accomplished in these gravely ill patients is greatly facilitated by the percutaneous internal jugular approach.

TECHNIQUE

A Wickbom needle (17 gauge 7 cm. thin walled needle) is used for the jugular puncture. We have also used a thin wall 18 gauge 4¾ inch needle.* A flexible tipped guide wire (OD 0.0315 inches) passes through the needle. We have used two catheter systems; one, with a closed tip catheter and the second, with an open tip. The closed end catheters that we have used have been a thin wall teflon with an inner diameter of 0.064 inches and a woven dacron thin wall catheter with an inner diameter of 0.058 inches. The catheter is introduced through a tapered ultrathin teflon sheath which is first inserted over a tapered teflon open end introducing catheter.[1,2] The open end catheter system utilizes a small P90 radiopaque polyethylene catheter inside a large P240 radiopaque polyethylene catheter. The P90 catheter, being 10 cm. longer and having a preformed curve, can be made to change the degree of curvature of the advancing end by altering the amount it protrudes from the larger catheter.[3]

Image intensification is employed for positioning the catheter and a single plane film changer is required.

With the patient supine, the chin is extended and the area from the angle of the right mandible to the right clavicle is prepared and draped. The right sided approach allows a straight course to the right atrium. The shoulders should not be elevated to

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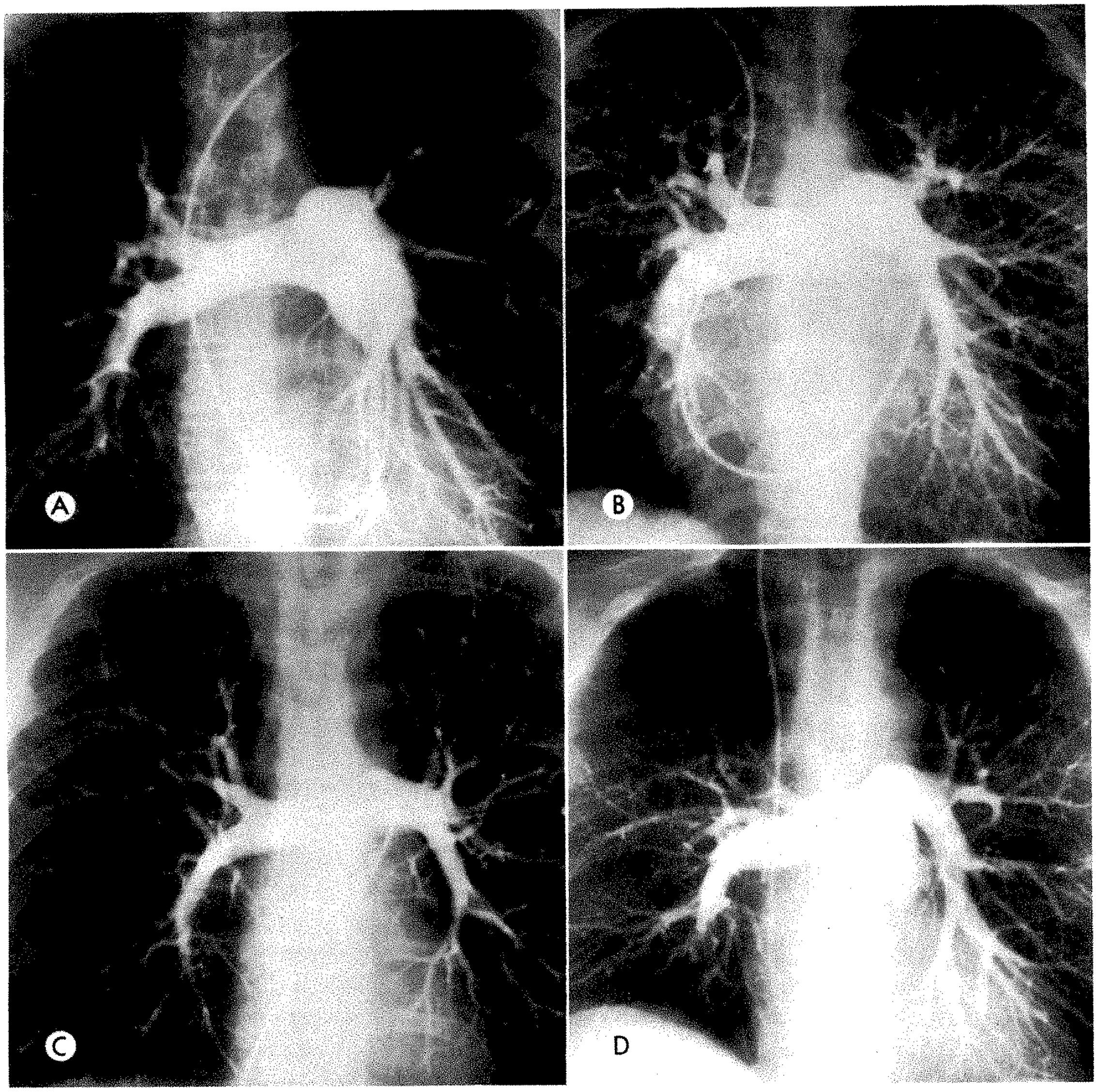

Fig. 1. Four approaches to pulmonary angiography. (*A*) Left antecubital approach utilizing a long continuous curve of the catheter. (*B*) Right antecubital approach with a double curve. (*C*) Femoral approach with S-shaped curve. (An undesirable vein to enter if thromboembolic disease is suspected.) (*D*) Simple single curve with jugular approach.

facilitate neck extension since the venous pressure will be decreased and the vein will collapse.

Figure 2 diagrammatically demonstrates the immediate lateral position of the internal jugular vein to the internal and common carotid arteries. The operator's finger is placed 2 fingerbreadths below the angle of the mandible and directly over the carotid pulse. The skin and subcutaneous tissues just lateral to the pulse are infiltrated with 1 per cent Xylocaine and a small stab wound is made in the skin to facilitate easy passage of the catheter.

A plain tip syringe containing 5 cc. of 1 per cent Xylocaine is attached to the puncture needle. A 45° angle with the skin is maintained and the needle is directed through the stab wound just lateral to the finger overlying the carotid pulse. Xylo-

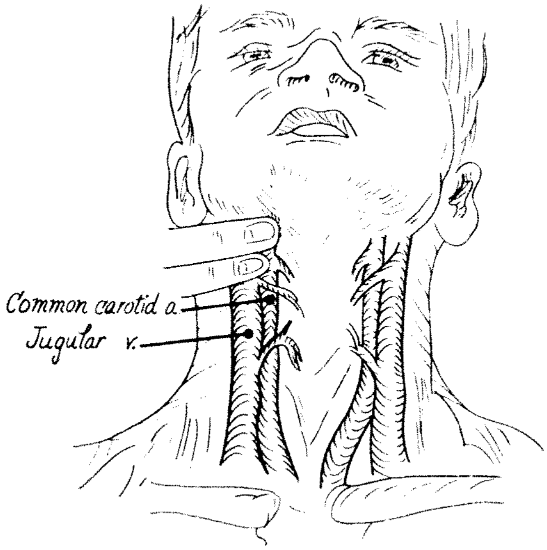

Fig. 2. Anatomic location of internal jugular vein. The needle is introduced just lateral to the carotid pulse and 2 fingerbreadths below the angle of the mandible.

caine is injected periodically to relieve discomfort. Constant aspiration is used and a vigorous flow of dark venous blood is seen on entrance into the jugular vein. A 2 or 3 cc. test injection of contrast medium under image intensification will verify the needle's position.

If an open end catheter system is employed, the regular Seldinger method is used to place the catheter in the vessel.

If a closed end catheter is desired, preliminary preparations are made by placing a teflon sheath over a short tapered, open end, introducing catheter. By Seldinger technique the open end introducing catheter and sheath are threaded into the vein over the guide wire. The sheath is held in position and the introducing catheter withdrawn; the closed end catheter is then inserted through the sheath into the vessel and the sheath is slipped out of the skin onto the closed end catheter. This method is essentially the same as that previously described for the introduction of percutaneous closed end cardiac catheters[1,2] except that in the catheterization of large veins, a teflon sheath can be used.

Upon removal of the catheter, gentle pressure for 3 to 5 minutes will control oozing. If the patient's condition permits, he is allowed to sit up immediately following the procedure to reduce venous pressure in the jugular vein.

All catheters introduced by the jugular route for pulmonary angiography should have a gentle distal curve so as not to pass directly into the inferior vena cava, but rather to slip easily through the tricuspid valve.

Originally, we used the closed end system to avoid the whip of the catheter tip seen with open end catheters at high injection pressures. However, with catheters of the same external diameter, the radiopaque polyethylene* has an inner diameter of 0.013 of an inch larger than the thin wall woven dacron and 0.007 of an inch larger than the thin wall teflon. The internal jugular approach does not require a long catheter so that the catheter we are presently using is only 50 cm. long. These two factors make it possible to obtain a high flow rate with relatively low injection pressure. Using this catheter, the delivery rate of viscous angioconray at a recorded pressure on the Gidlund injector of 3 kg./cm.^{2} is 20 cc./sec. The same catheter under the same conditions delivers 25 cc./sec. of water. We have used angioconray for most of our injections and obtain satisfactory opacification with this delivery rate. The catheter does not recoil during selective injections in the right and left pulmonary arteries.

MATERIAL

Since December 1965 we have performed 20 pulmonary angiographies via the percutaneous jugular approach. The indication in 18 of the cases was the suspicion of pulmonary emboli, whereas the studies in the other 2 cases were part of a tumor workup. A closed end catheter was used in 14 cases and an open end catheter was used in the remainder. The majority of our patients had rheumatic valvular disease and associated pulmonary hypertension.

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COMPLICATIONS

The only complication related to this approach to date has been one case with minimal bleeding from the puncture site 1 hour following the procedure. This was easily controlled by digital compression.

The catheter was passed through the pulmonary outflow tract in 1 patient with no untoward result, but this could not be ascribed to the approach used.

DISCUSSION

While the antecubital venous cutdown has been a reliable and tested method for pulmonary angiography, we feel that the percutaneous jugular approach is a valuable alternative method with certain advantages. The reliable position of this vein facilitates speedy accomplishment of an emergency angiogram. This vessel is many times larger in diameter than the antecubital vein thus allowing the introduction of larger catheters with greater flow rates. In fact, we feel that it is large enough to accept a sheath through which emergency pacemaker leads could be placed without the need of isolating the vessel surgically. Anatomically, the right jugular vein is situated in a more direct line with the heart than either the antecubital or femoral veins, thereby avoiding many catheter directing problems.

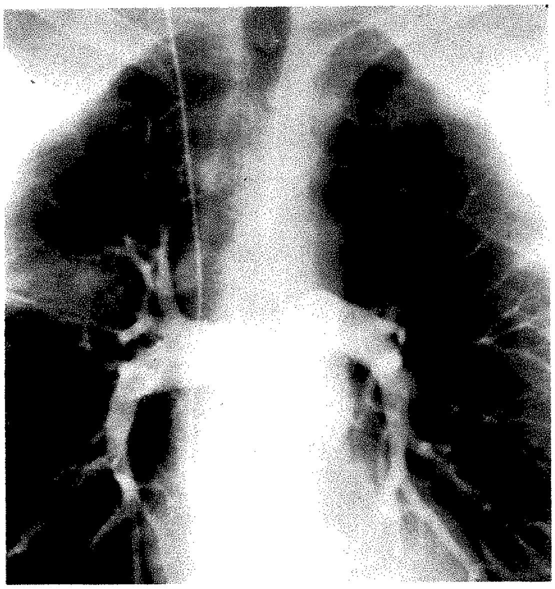

Fig. 3. Angiogram of patient with normal pulmonary artery pressure. Note the excellent visualization.

With identical conditions, the opacifica-

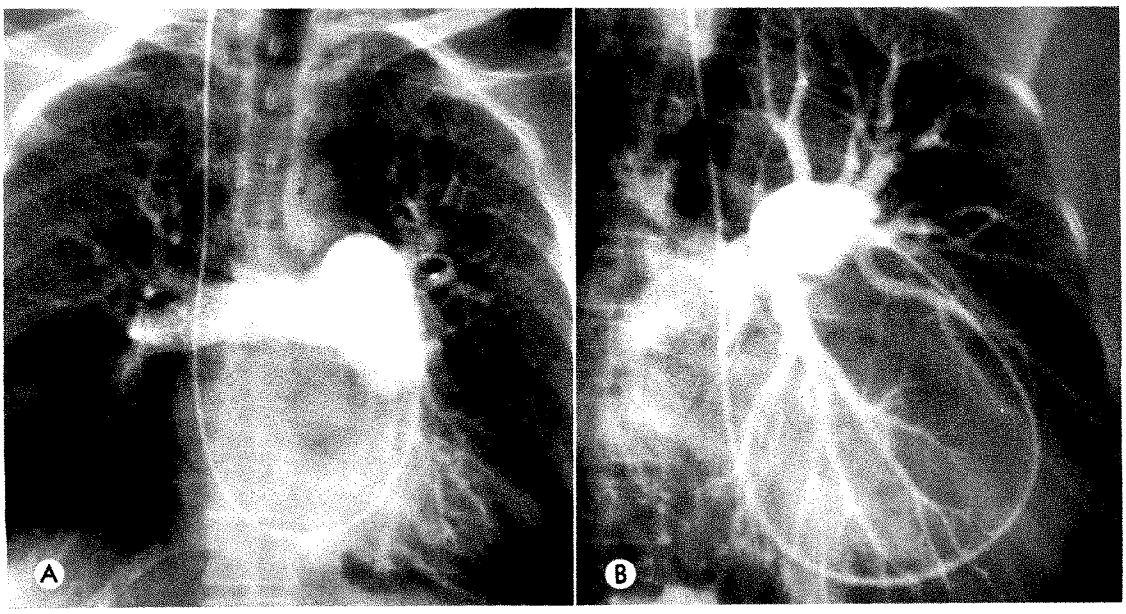

Fig. 4. Mitral heart with main pulmonary artery pressure of 75 mm. Hg. (*A*) Main pulmonary artery injection. Note poor opacification. (*B*) Selective left pulmonary artery injection in same patient as in *A*. Opacification and detail are greatly improved by the selective injection.

tion of the pulmonary bed in the patient with pulmonary hypertension is considerably poorer than in the normal. Figure 3 is the angiogram obtained in the workup of a bronchogenic carcinoma. The main pulmonary artery pressure was normal. Figure 4*A* is the main pulmonary artery injection in a patient with mitral valvular disease and a main pulmonary artery pressure of 75 mm. Hg. The difference in detail and quality of opacification is self evident, yet the technical factors were not dissimilar. This has been seen repeatedly and we now use selective right and left pulmonary artery injections with more frequency (Fig. 4*B*).

CONCLUSION

A technique for the percutaneous approach to pulmonary angiography using the internal jugular vein is described. It can be accomplished quickly in the gravely ill patient due to the large size of the vessel and its reliable anatomic location. Either open or closed end catheters can be used. With this method, selective right and left pulmonary artery injections can be more easily performed thereby allowing more detailed visualization of the pulmonary vascular bed.

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SELECTIVE AORTOGRAPHY, THE DEFINITIVE TECHNIQUE, FOR DIAGNOSIS OF DISSECTING ANEURYSM OF THE AORTA*

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IN THE past two decades, many significant reports dealing with dissecting aneurysm (hematoma) of the aorta have appeared in the literature.[11,16] The term, dissecting aneurysm, was first used by Laennec in 1819, but only recently, probably because of refinements in diagnosis and therapy (surgical and medical), has the entity received increasing attention.[1,6,7,14,17,22]

During the past 4 years, 18 consecutive patients with dissecting aneurysms (hematoma) of the aorta have been studied at this center by means of selective aortography. The chief findings in these cases, the technique of aortographic examination, and the roentgen criteria for the definitive diagnosis of the disease, are the main reasons for this report.

MATERIAL AND METHODS

Eighteen patients were examined 19 times (1 patient was re-examined 9 months after the initial diagnosis was made). Percutaneous transfemoral or transaxillary selective techniques were used with advancement of a gray or yellow Ödman-Kifa end- and side-hole catheter. Positioning of the catheter was made under roentgenoscopic control using image intensification and television monitoring. Test (hand) injections of 5 to 10 ml. of 50 per cent hypaque, aided precise location of the catheter. Selection of the site of arterial puncture, whether axillary or femoral, depended upon the presence and quality of peripheral pulses. Injections of 1 ml. of contrast material (hypaque 75 per cent or angioconray) per kg. of body weight, up to a total dose of 50 to 60 ml., were made using the Gidlund injector with pressures of 5 to 7 kg.[2] One or more injections of contrast material were made, depending upon the condition of the patient and the need for additional information. In no instance was it necessary to terminate the examination because of deterioration of the patient's condition. Serial films of the chest were exposed in biplane, frontal and lateral views, or in the left anterior oblique projection using a Schönander film changer. The speed of exposure was 6 films per second for 2 to 3 seconds, and 5 to 7 additional exposures at the rate of 1 per second. In the majority of cases,

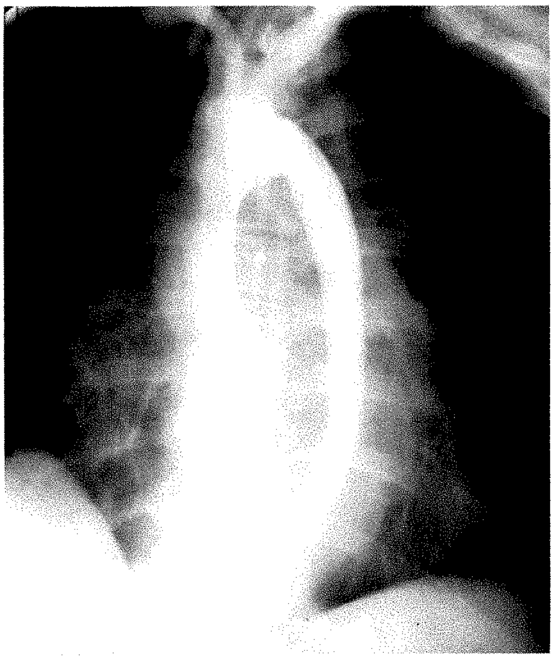

Fig. 1. Thoracic aortogram showing opacification of distorted and narrowed true channel with wide surrounding soft tissue density due to thrombosed false channel.

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Table I

CLINICAL, ROENTGENOGRAPHIC, AND PATHOLOGIC FINDINGS IN AORTIC DISSECTION

Case No.	N.Y.H. No. and Date of Study	Sex and Age	Blood Pressure on Admission (mm. Hg)	History of Hypertension	Chief Complaint	Physical Findings	Conventional Roentgenograms	Time from Onset of Symptoms to Aortography	Selective Aortography	Operations, Results, Follow-up, and Autopsy
I	925404 10/13/62	M 42	240/120	Yes	Abdominal pain of 6 hours' duration	Blowing systolic murmur (Grade 3), thrill, and bruit over right femoral artery	Widening of thoracic aorta and mediastinum, generalized cardiac enlargement	1 day	Dissection began above aortic valve, involved ascending and descending thoracic aorta, entire abdominal aorta, and right renal artery (Fig. 1)	Death on 10/21/62, 8 days following operation. Autopsy revealed dilatation and hypertrophy of heart, pericarditis and dissecting aneurysm of the thoracic aorta to iliac arteries
II	545517 1/6/63	M 55	200/140	Yes	Pain in midback radiating to lumbar area and diaphoresis	Bruit over left femoral area	Left pleural effusion, widening and irregularity of thoracic aorta, and cardiomegaly	6 hours	Dissection began above aortic valve, and involved ascending and descending thoracic aorta	Uncontrollable rupture of aneurysm during exploratory thoracotomy, dissection extended to origin of great vessels. Autopsy confirmed diagnosis
III	477745 8/8/63	M 56	150/85	Yes	Dyspnea and left-sided back pain, 2 weeks	Slight abdominal tenderness, all pulses palpable	Tortuous thoracic aorta, and normal heart	4 weeks	Dissection began distal to left subclavian artery	Became anuric after operation and died next day. Autopsy showed dissection 2 cm. distal to left subclavian artery, hemothorax, hemopericardium, and atelectasis of left lower lobe
IV	903096 8/22/63	M 47	150/60	Yes	Chest pain	Enlarged heart, aortic diastolic murmur (Grade 2), and systolic murmur at aortic and apical areas	Marked widening of thoracic aorta, and enlargement of left ventricle (Fig. 2*A*)	2 days	Dissection began above aortic valve, with aortic insufficiency and involvement of ascending and descending thoracic aorta (Fig. 2, *B* and *C*)	Operation 8/27/63, died on 9/4/63. Autopsy revealed hypertrophy of heart, nephrosclerosis, and fresh intracerebral hemorrhage with subarachnoid extension
V	964009 1/13/64	M 60	130/80	No	Back pain radiating to abdomen, weakness, and fever, 24 hours	Systolic murmur over aortic area	Widening, tortuosity of thoracic aorta, and slight enlargement of left ventricle	25 days	Dissection began distal to left subclavian artery, and extended into abdominal aorta and right common iliac artery (Fig. 3, *A* and *B*)	Surgery contraindicated because of congestive heart failure. Last clinic visit 5/8/65, condition unchanged
VI	728751 3/27/64	M 63	170/88	Yes	Epigastric pain radiating to left chest, 2 weeks	Enlarged heart with good and equal pulses	Marked widening of mediastinum, and aortic knob, irregular descending thoracic aorta, and cardiomegaly	2 weeks	Dissection began distal to left subclavian artery, extended into abdominal aorta and right common iliac artery.	Improved following transection of aorta and construction of a reentry window in the abdominal aorta, discharged 4/14/64
VII	579560 6/3/64	M 60	190/104	Yes	Pain in epigastrium and back	Normal pulses, no murmurs	Prominent aortic knob, and normal heart	3 weeks	Dissection began distal to left subclavian artery, extended into abdominal aorta and left common iliac artery	Repair of dissection at another hospital 6/19/64. Readmitted 3/21/65, with chest pain. Discharge diagnosis angina pectoris due to myocardial ischemia. Last seen 11/5/65, condition unchanged
VIII	977267 6/24/64	F 57	120/80	No	Pain in back	Enlarged heart, systolic murmur at apex, and diminished femoral pulses	Widening of thoracic aorta, and cardiomegaly	Chronic—duration?	Dissection began distal to left subclavian artery, involved abdominal aorta, superior mesenteric, and left renal arteries	Surgery refused by patient
IX	621522[20] 7/20/64	F 48	126/80	No	Dyspnea and heart failure	Neck veins distended, lung bases dull with moist rales, edema of extremities and enlarged liver	Left pleural effusion, and large left ventricle and atrium (rheumatic heart disease), normal thoracic aorta	7 months (immediately following open heart surgery)	Dissection began distal to left subclavian artery and followed femoral cannulation during open-heart resection of aortic stenosis	Readmitted 9 months after open-heart aortic valvulotomy with atrial fibrillation, atrioventricular dissociation, and nodal tachycardia, rate 140. After discharge had heart failure and died in nursing home 6 months later; no autopsy
X	990032 9/1/64	M 63	180/80	No	Pain in right jaw radiating to head and pain in left sacroiliac area, 24 hours	Harsh systolic murmur over aortic area, diastolic murmur 3rd left interspace, and bruit over both femoral arteries	Prominent aortic knob, and cardiomegaly	2 days	Dissection began above aortic valve, involved ascending aorta, caused aortic insufficiency, involved descending thoracic aorta, entire abdominal aorta, both renal, and both common iliac arteries	Patient died of shock during operation. Autopsy showed dissection 2 cm. above aortic cusps, hypertrophy of heart, and generalized arteriosclerosis; dissection extended into internal and external iliac arteries

Case No.	N.Y.H. No. and Date of Study	Sex and Age	Blood Pressure on Admission (mm. Hg)	History of Hypertension	Chief Complaint	Physical Findings	Conventional Roentgenograms	Time from Onset of Symptoms to Aortography	Selective Aortography	Operations, Results, Follow-up, and Autopsy
XI	1007049 2/23/65	M 61	210/110	Yes	Subxyphoid pain radiating to back, hyperesthesia, paresis, and cyanosis of lower extremities	Systolic murmur (Grade 2/6) over aortic valve, pulses palpable and equal	Widening of mediastinum and aortic knob, with minimal cardiomegaly	1 day	Dissection began distal to left subclavian artery, extended into abdominal aorta, and involved left renal artery just above a fusiform abdominal aneurysm (Fig. 4)	Operated on day after admission; dissecting aneurysm began at left subclavian artery; ventricular fibrillation during operation. Autopsy revealed fusiform aneurysm of abdominal aorta, hypertrophy of heart, and multiple thoracic dissections without extension into visceral vessels
XII	1008995 3/13/65	M 50	160/100	No	Interscapular pain and generalized abdominal pain, 12 hours	No murmurs, peripheral pulses palpable and equal	Widening of thoracic aorta, and cardiomegaly	2 weeks	Dissection began distal to left subclavian artery, involved abdominal aorta, superior mesenteric, and left renal arteries (Fig. 5)	During operation for replacement of aorta, bleeding disthasis developed; patient became hypotensive and had cardiac arrest. Autopsy showed hypertrophy of heart and dissecting aneurysm
XIII	1011940 4/15/65 1/31/66	M 59	172/108	Yes	Substernal chest pain radiating to back and left flank, 2 weeks	Cardiomegaly, hepatomegaly, holosystolic murmur (Grade 3/4) radiating to back and left axilla, and left flank bruit	Left pleural effusion and marked widening of mediastinum and thoracic aorta, particularly aortic knob, and cardiomegaly (Fig. 6*A*)	2 weeks	Dissection began distal to left subclavian artery, involved and re-entered right renal artery and abdominal aorta 1 cm. distal to it. Second study, 9 months later, shows increase in size of false lumen involving left renal artery (Fig. 6, *B–H*)	Widespread aneurysm contraindicated surgery and patient was treated with antihypertensive drugs. Re-examination 8 months later showed further enlargement of false channel. Died day following operation at another hospital (6/23/66). No autopsy
XIV	569558 7/31/65	M 59	220/160	Yes	Dyspnea and interscapular pain	Enlarged heart, no murmers, all pulses palpable except dorsalis pedis	Dilatation and tortuosity of thoracic aorta, left ventricular enlargement	5 days	Dissection began distal to left subclavian artery with almost complete thrombosis of false channel except for small ulcer-like communications with true channel (Fig. 7, *A* and *B*)	Operation on 8/3/65, died next day. Autopsy showed dissection and acute myocardial infarction
XV	1029141[19] 9/30/65	F 57	120/80	Yes	Syncope and unconsciousness	Holosystolic murmur (Grade 1/6) at apex to axilla and systolic murmur (Grade 2) over aorta, radiating to carotid arteries	Dilated ascending aorta, and normal heart	16 months	Dissection began above aortic valve, involved entire thoracic and abdominal aorta, and both common iliac arteries (Fig. 8, *A*, *B*, and *C*)	Operation not advised because patient was asymptomatic
XVI	911246 8/4/66	F 61	210/110	Yes	Pain in neck radiating to ears and back	Diminished right radial pulse, absent right femoral pulse, bruit over lower thorax, lumbar spine, and neck, systolic murmur (Grade 3/4) over aortic area	Widening of thoracic aorta	3 months	Dissection began just above aortic valve, involved ascending and descending thoracic aorta, entire abdominal aorta, and left common iliac artery; left renal artery communicated with 1 patent channel; other visceral arteries supplied by second channel (Fig. 9, *A–D*)	Operation not advised because of extensive dissection. Last seen 9/21/66, had intermittent back pain, blood pressure 110/80 mm. Hg
XVII	1016149 12/19/66	M 67	168/92	Yes	Chest pain	Distended neck veins, harsh apical systolic murmur, and cardiomegaly to percussion	Marked enlargement of proximal descending thoracic aorta, and cardiomegaly	3 days	Dissection began distal to left subclavian artery and involved entire abdominal aorta (Fig. 10, *B* and *D*)	Death on 1/1/67. Autopsy revealed cystic medial necrosis of aorta, dissection began just distal to origin of left subclavian artery and extended to the bifurcation of the aorta
XVIII	1074184 12/21/66	M 50	230/100	Yes	Sudden onset of severe back pain and numbness of right foot	Diaphoresis, apical systolic murmur (Grade 1/6)	Normal heart, and aortic shadow	3 hours	Dissection began distal to left subclavian artery and involved entire abdominal aorta (Fig. 11, *A* and *B*)	Transferred to this hospital 10 days following insertion of abdominal aortic graft. Selective aortography and abdominal aortography performed at this hospital 12/21/66. Treated conservatively with antihypertensive drugs; improved and discharged on 4/6/67

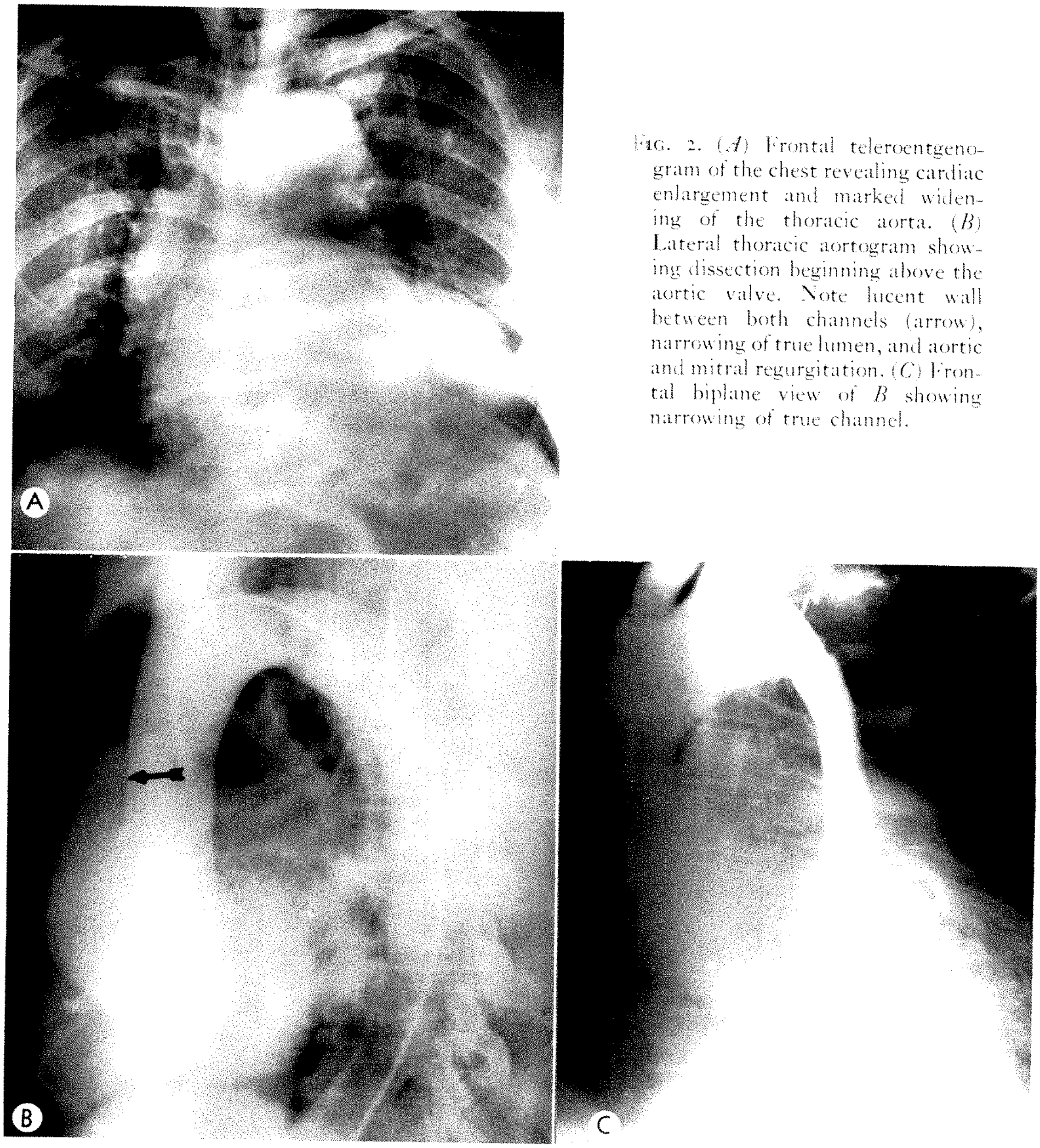


FIG. 2. (*A*) Frontal teleroentgenogram of the chest revealing cardiac enlargement and marked widening of the thoracic aorta. (*B*) Lateral thoracic aortogram showing dissection beginning above the aortic valve. Note lucent wall between both channels (arrow), narrowing of true lumen, and aortic and mitral regurgitation. (*C*) Frontal biplane view of *B* showing narrowing of true channel.

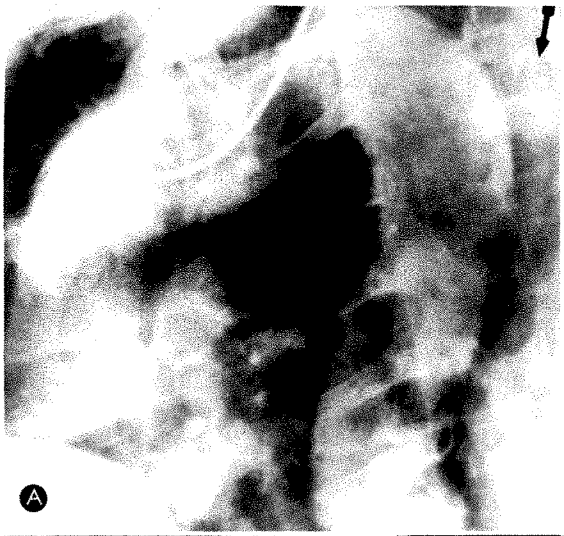
the abdominal aorta was also studied in the frontal projection.

CASE REPORTS

Table I lists the clinical, conventional roentgenographic, and selective aortographic data of 18 consecutive patients who had a definitive diagnosis of dissecting aneurysm.

RESULTS

Fifteen patients were men and 3 were women, a ratio of 5 men to 1 woman (Table I). The ages ranged from 42 to 69 years, the average was 56.6 years; 13 patients (72 per cent) had a history of hypertension. The time from onset of symptoms to aortography ranged from 6 hours to 16 months, with 14 patients being examined within 4



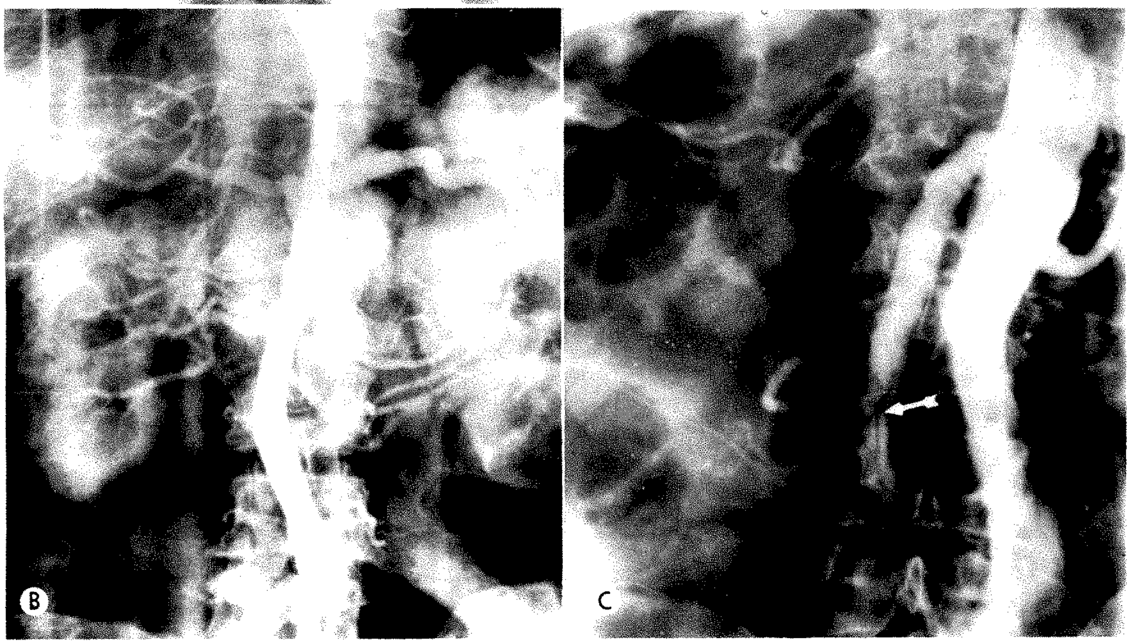


Fig. 3. (*A*) Thoracic aortogram showing almost complete thrombosis of false channel (arrow). (*B*) Abdominal aortogram via transaxillary route revealing a single narrow true channel which filled the celiac axis and branches, right renal, lumbar, and some branches of the mesenteric arteries. (*C*) Abdominal aortogram via transfemoral route showing a large false channel which supplied the left kidney, superior mesenteric artery, and some branches of the celiac axis. Note lucency and double lumen of superior mesenteric artery (arrow).

weeks following onset of symptoms. Three patients had symptoms relating to the dissection ranging from 6 to 16 months prior to aortography. Although 16 of 18 patients gave a history of pain, 1 patient had only dyspnea and heart failure (Case IX),[20] another only syncope (Case XV; Fig. 8, *A-C*).[19] Physical findings varied; the majority of patients, however, had either systolic and/or diastolic murmurs over the aortic valve area, peripheral bruits, or diminished pulses (Table 1).

Conventional roentgenograms of the chest were obtained in every patient. In 7 patients (41 per cent) the diagnosis was suspected because of mediastinal and aortic widening or irregularity (Fig. 2*A*, 6*A*, and 10*A*). In 1 of these cases there was also a left hemothorax (Fig. 6*A*). In none of the patients could the full extent of the dissection be predicted on the basis of conventional chest roentgenograms. Surgery was undertaken in 10 patients; 7 deaths occurred during and immediately after opera-

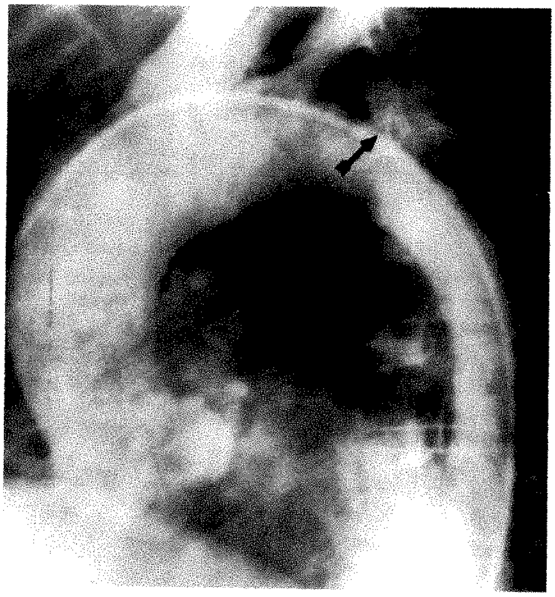


FIG. 4. Oblique thoracic aortogram showing incomplete thrombosis of the false channel with local extravasation of contrast medium at site of intimal tear (arrow).

tion. Three other patients died before therapy was instituted. In 4 patients (Case V, VIII, IX, and XV), all of whom had been studied 4 or more weeks after the onset of symptoms, surgery was either refused or not offered the patient. All but 1 of these patients (Case XI) were alive 1 to 3 years following the diagnosis of dissection. Another patient (Case XIII) was treated with antihypertensive drugs, and re-examined because of increasing back pain 9 months later. Marked increase in the size of the false lumen was found at the second examination (Fig. 6*H*). The patient was referred elsewhere for surgery, and died soon after operation.

Aortography was made with the percutaneous catheter technique in all patients. The abdominal aorta was examined in 15 patients. The false channel was thrombosed in the thorax in 6 patients. In 4 of these 6 patients, the abdominal aorta contained a double lumen; in 2 other cases the abdominal aorta was not examined. Diagnostic (full dosage) injections of contrast medium into the false channels were made in 6 patients (1 patient was also re-examined in this manner) without complication.

DISCUSSION

The autopsy incidence of dissecting aneurysm varies in different reports, but is in essential agreement with the figures of Holland and Bayley,[13] and Brindly and Stembridge[3] (1 in 381 postmortem examinations). Although aortic dissection has been reported in a 14 month old infant and a woman close to 100 years of age, the largest number of cases occur between the ages of 40 and 70 years. Only 1.4 per cent of the 505 cases of dissecting aneurysms reported by Hirst and colleagues[11] occurred below the age of 20 years. In the same review, 63 per cent of the patients had a history of hypertension. This is in agreement with our series (Table I). In addition to hypertension, which appears to be the most important predisposing cause of dissecting hematoma, the disease has been associated with cystic medial necrosis of the aorta, Marfan's sydrome, coarctation of the aorta, Turner's syndrome, and pregnancy.

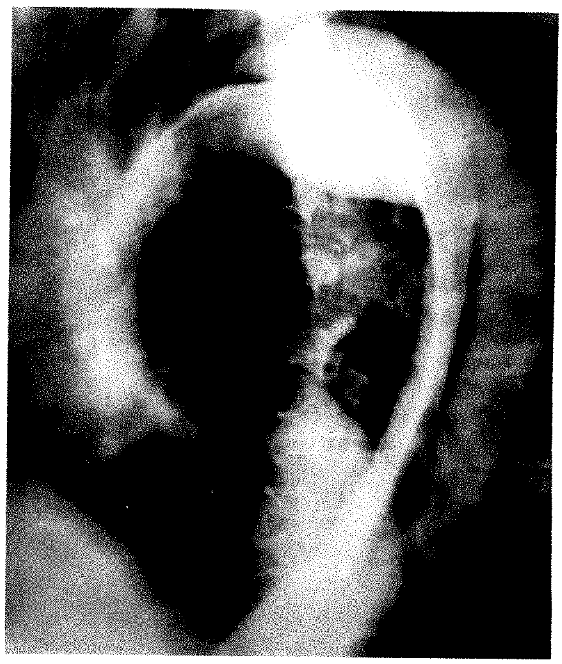


FIG. 5. Oblique thoracic aortogram showing double-barrelled aorta with the two opacified channels separated by a lucent wall.

It is generally agreed that medial cystic degeneration of the aorta is an essential feature of aortic dissection. Rupture of vasa vasorum giving rise to an intramural hematoma is probably the initial lesion in many cases, and the intimal tear, which is usually present, is believed to be secondary to the intramural dissection. Most dissections begin either in the ascending aorta, or just distal to the left subclavian artery. Although the classic clinical description of this entity is that of severe, tearing chest and back pain radiating to the throat, abdomen, or extremities, in some cases pain may be absent or masked by syncope (Case xv, Fig. 8, *A-C*).[19] Levinson and colleagues[16] were unable to secure a history of pain in 22 per cent of their cases. Other symptoms and physical findings, typically associated with dissecting aneurysm, were also present in our series (Table 1).

The roentgen criteria for diagnosis of dissecting aneurysm on conventional roentgenogram of the chest have been previously described,[8,23] and include increase in aortic width on sequential examinations, an aortic wall width of more than 1 cm. as measured from intimal calcification to the outer aortic border, mediastinal, lung and pleural changes, a localized hump just distal to the

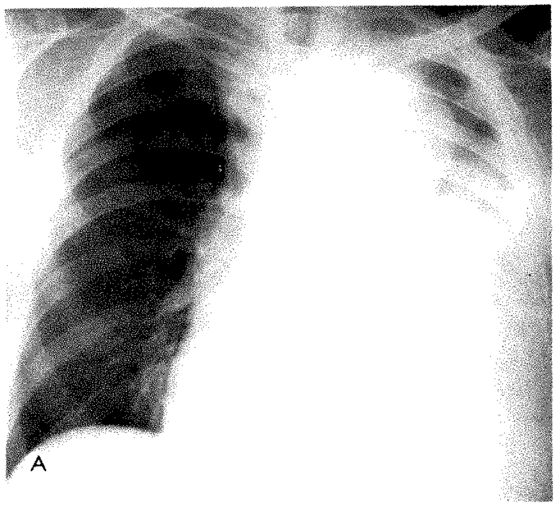


Fig. 6. (*A*) Conventional teleroentgenogram showing marked enlargement of the aortic knob and huge left hemothorax.

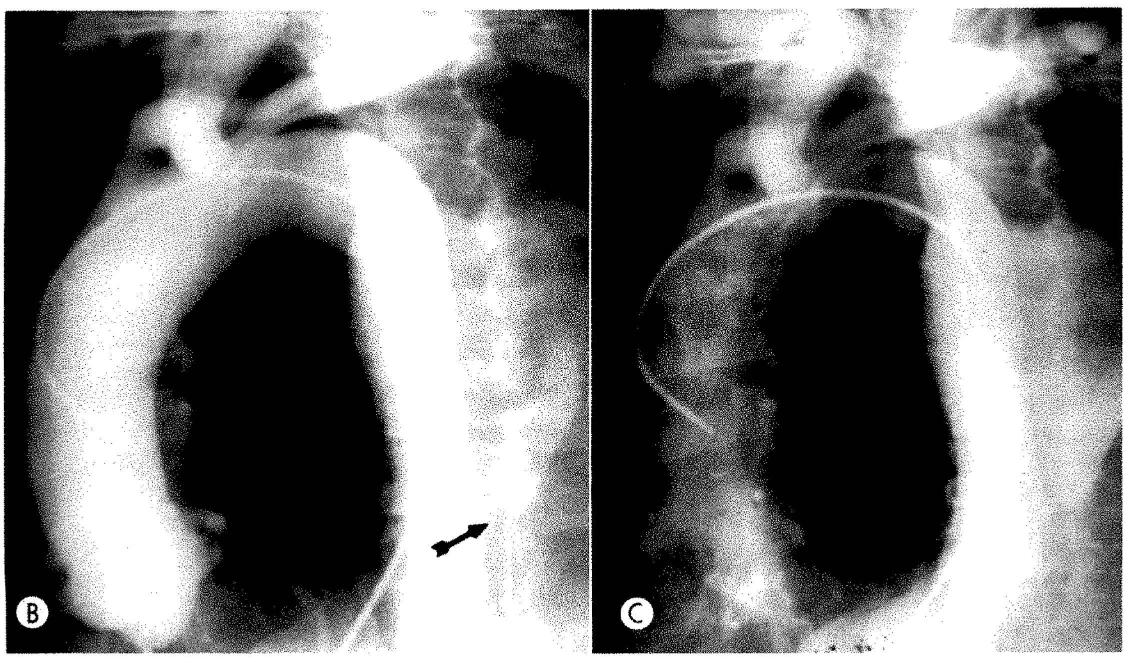


Fig. 6. (*B*) Oblique thoracic aortogram (1 sec.) showing extravasation of contrast material into false lumen at site of intimal tear in descending aorta (arrow). (*C*) Aortogram (3 sec.) showing that the true lumen empties, whereas the false lumen has become more opaque.

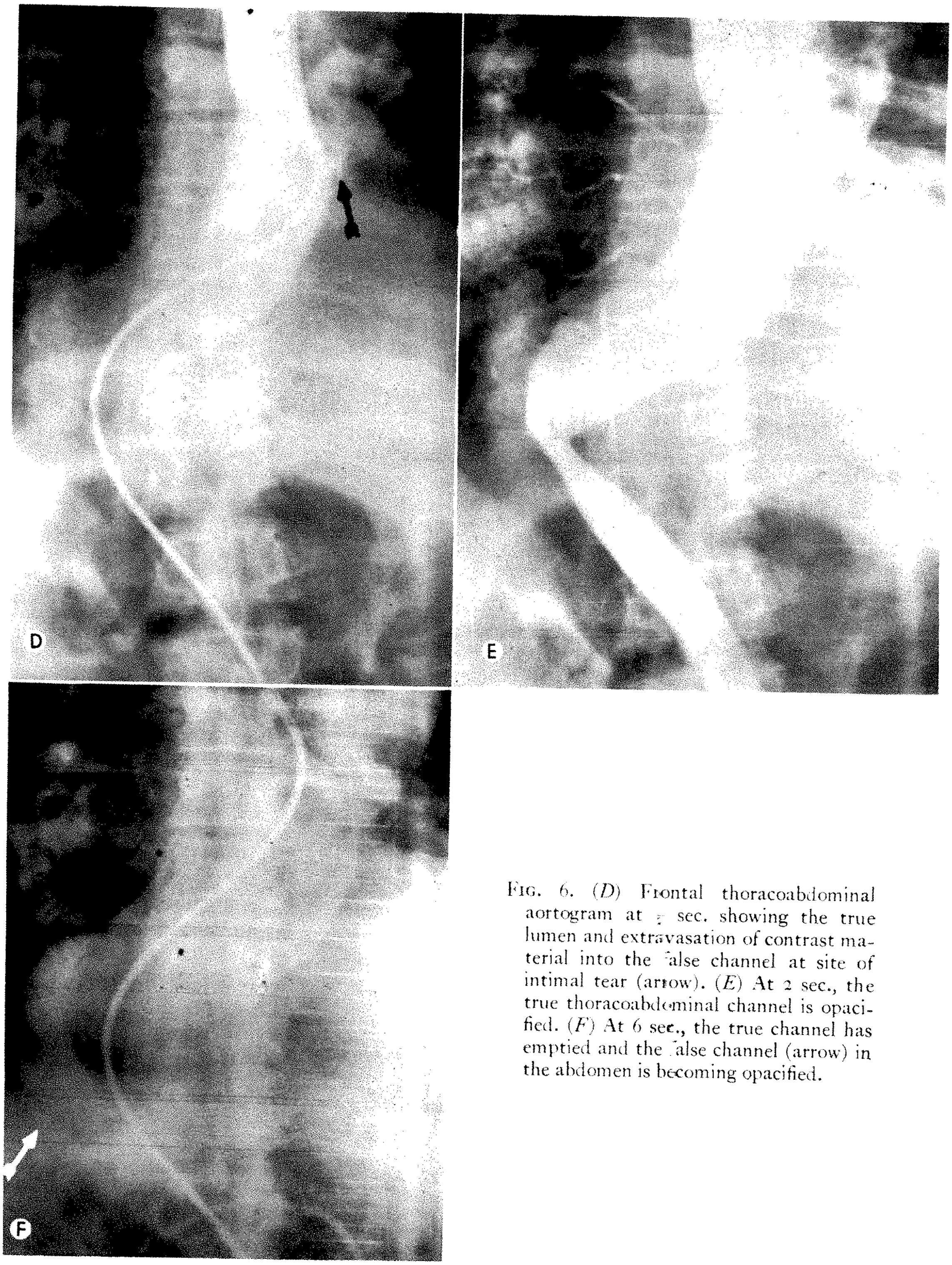


Fig. 6. (*D*) Frontal thoracoabdominal aortogram at ½ sec. showing the true lumen and extravasation of contrast material into the false channel at site of intimal tear (arrow). (*E*) At 2 sec., the true thoracoabdominal channel is opacified. (*F*) At 6 sec., the true channel has emptied and the false channel (arrow) in the abdomen is becoming opacified.

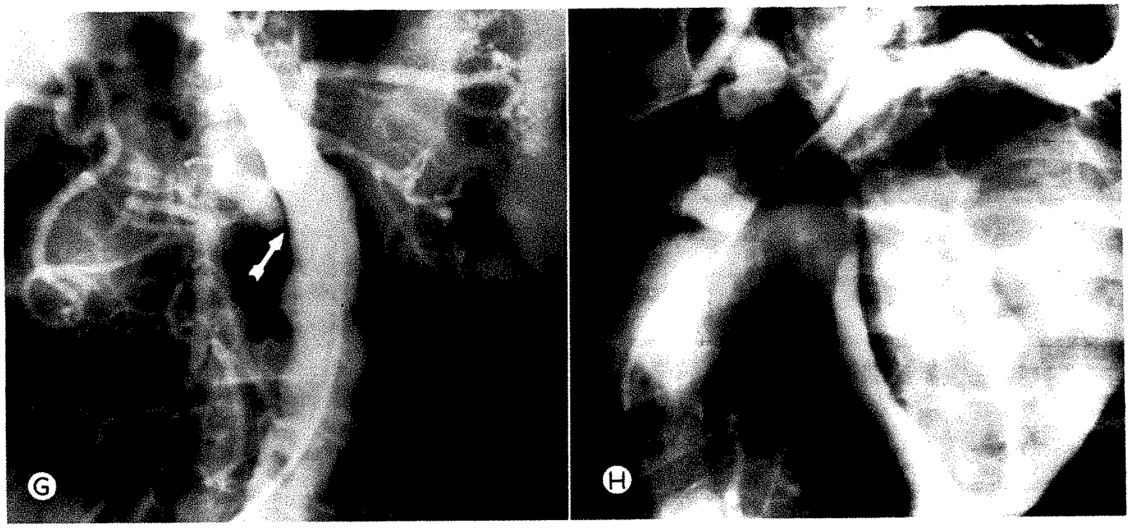


Fig. 6. (*G*) Abdominal aortogram showing filling of false channel at re-entry point just below the right renal artery. Note lucent wall between both lumina (arrow). (*H*) Oblique thoracic aortogram (9 months later) showing marked increase in size of false lumen.

origin of the left subclavian artery, and disparity in size of the ascending and descending aorta. These findings are often suggestive of dissecting aneurysm, but the definitive diagnosis depends upon contrast visualization of the aorta and demonstration of a "double barrel" aorta, the site of intimal tear, or re-entry point into the aorta or one of its branches. Intravenous aortography can be made with relative ease and minimal risk.[18] There are, however, several difficulties when this method is used for diagnosis of dissecting aneurysms. These are, poor detail of the sites of rupture and re-entry as compared to direct aortography, and the occasional intense opacification of adventitial or neighboring vessels which may simulate extraluminal contrast material in a false aortic channel and lead to the mistaken diagnosis of dissecting aneurysm.[15] In the intravenous method it is important to secure an accurate circulation time; when it is markedly prolonged because of severe heart failure or shock, undue dilution and poor aortograms may result. Also, in order to visualize the abdominal aorta, a second large bolus of contrast material may be necessary. For these reasons, selective aortography is recommended. The percutaneous transfemoral[12,21] or right transaxillary routes[4] have been proposed as the methods of choice for diagnosis of dissecting aneurysm. While catheter aortography has not been accepted by all observers,[9,10] it would appear, however, that the best detail is offered by the selective approach (Fig. 1 to 12).

During the past 4 years, patients suspected of having a dissecting aneurysm have been routinely examined by catheter aortography at this center. Either or both the transfemoral or transaxillary routes have been used; the choice of which one to use was made by the roentgenologist after evaluation of the general condition of the patient and the quality of peripheral pulses. A good, pounding pulse was considered favorable for puncture, as opposed to a poor, thready pulse, or one in an extremity in which there was pain or numbness. Following percutaneous catheter insertion, careful manipulation and advancement of the catheter was made only during image intensification and television monitoring. Frequent, small (5 ml.) hand injections of 50 per cent hypaque were made prior to final positioning of the catheter. When the catheter was advanced via the femoral ar-

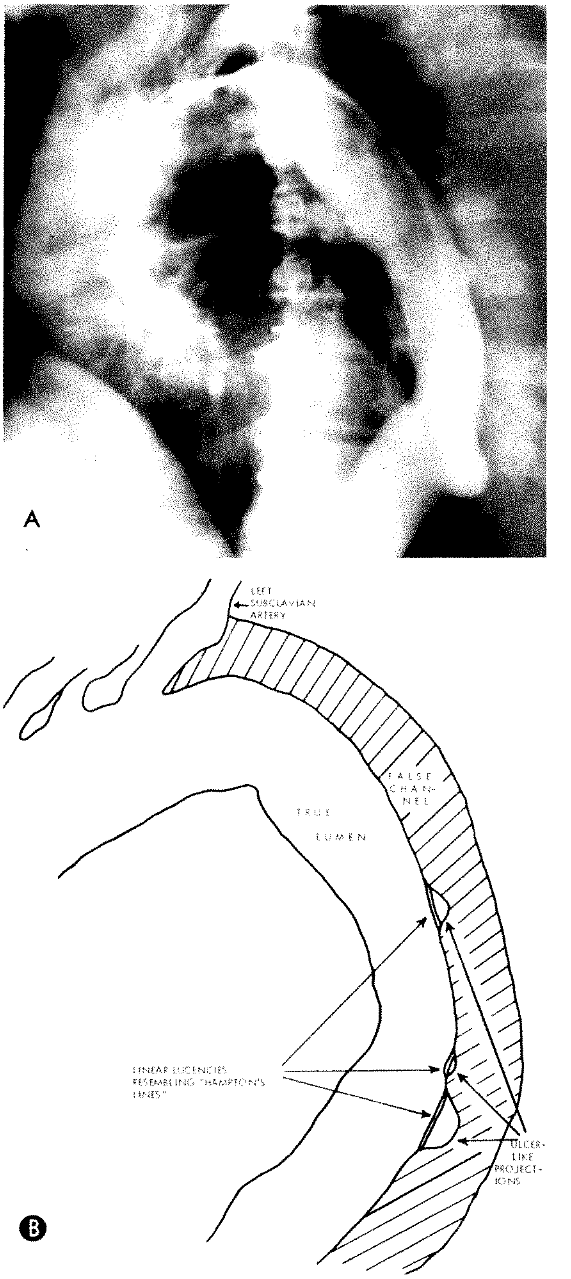


Fig. 7. (*A*) Oblique thoracic aortogram showing the thrombosed false channel. Note "ulcer-like" projections into false channel which represent sites of communication between the channels. (*B*) Diagram of *A*.

tery, the course and position of the catheter was similar to that described by Cramer and Amplatz.[5] Another significant finding on roentgenoscopy and roentgenography was failure to visualize the aortic sinuses with test injections when the catheter was in the supravalvular location. This indicates that the catheter is in the false lumen (Fig. 8*A*) of a dissection which involves the ascending aorta, but this should not discourage attempts to complete the examination. Injections of contrast material (50 ml. 75 per cent hypaque or angioconray) were made into the false channel in 6 of our cases, without rupture or complications. Therefore, it would appear that injection of contrast material via a catheter located in the false channel is tolerated.

The definitive diagnosis of dissection of the aorta can be made when both channels are opacified and a site of intimal tear visualized. The radiolucency between channels which represent the intima and inner two thirds of the media is seen only when the aorta is viewed in profile. Since dissections are often circumferential, these linear lucencies are not always parallel to the long axis of the aorta, but may appear to pass obliquely in different directions (Fig. 11*A*). Therefore, multiple views of the aorta are helpful and often necessary to determine the full extent of the dissection. Aortic insufficiency and coronary artery occlusions at their origins may be additional roentgen findings when the ascending aorta is involved. Distortion and narrowing of one of the opacified channels (Fig. 1; 2*C*; 5; 6, *B-D*; 9*A*; and 10*B*) are other important and common findings; if both channels fail to visualize, they are strongly suggestive of dissection. When there is no apparent intimal tear or communication between the aortic lumen and the dissecting hematoma, demonstration of a narrowed or distorted opacified channel, abnormal flow patterns to clinically viable viscera, and aortic valve insufficiency are highly suggestive of dissection, although not necessarily definitive. The false channel may be partially thrombosed, with only limited extravasation of contrast material at the site or sites of intimal tear (Fig. 4).

The false channel appeared thrombosed in the thoracic aorta in 6 patients (Fig. 3*A*). However, other, albeit subtle, changes

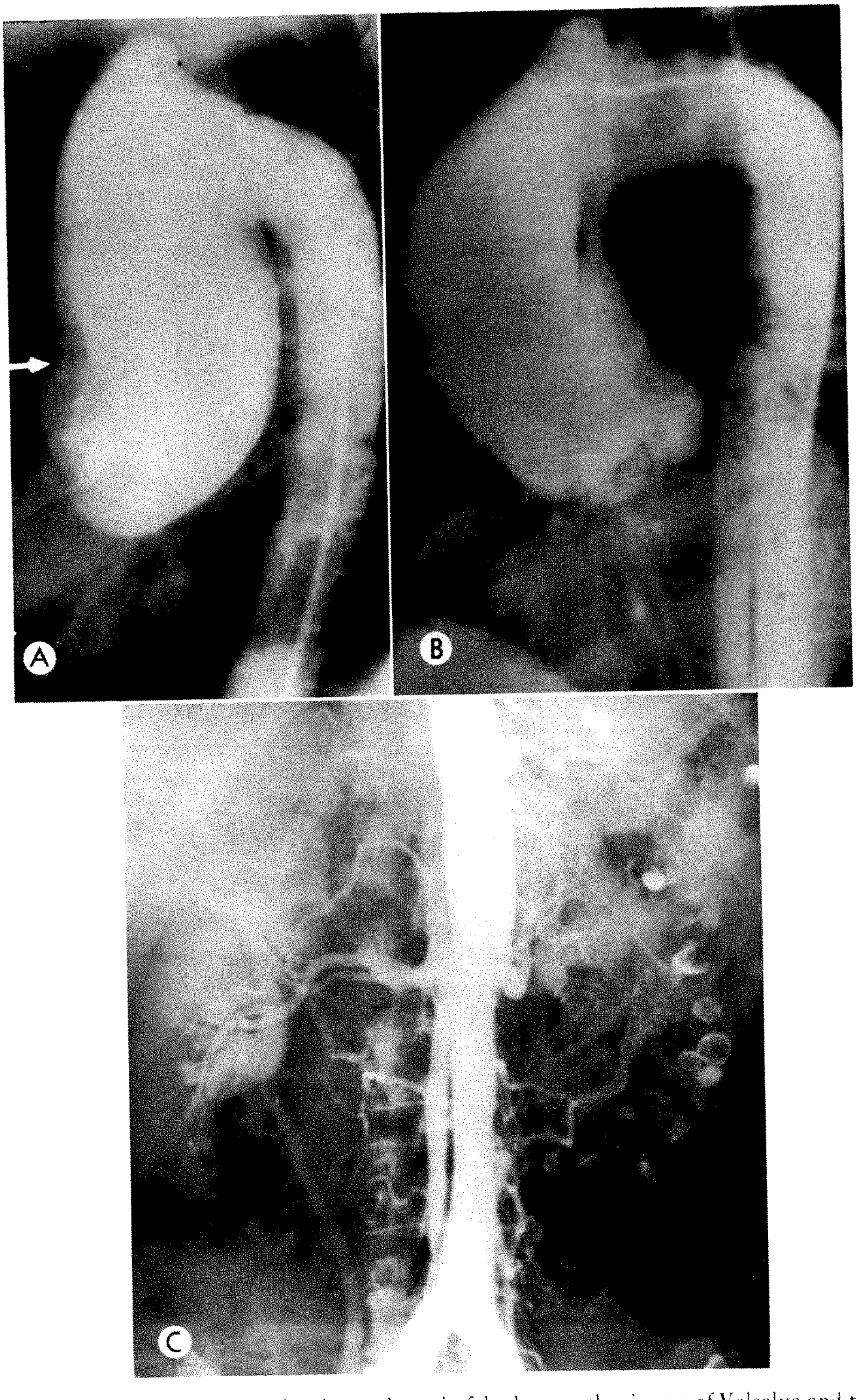


FIG. 8. (*A*) Right oblique aortogram showing catheter in false lumen; the sinuses of Valsalva and the coronary arteries are not visualized, and the site of intimal tear is represented by lucent defect where unopacified blood enters the false lumen (arrow). (*B*) Left oblique aortogram (in diastole) showing filling of the coronary sinuses. Note linear lucencies and dissection around the origins of the innominate and left common carotid arteries, and in the ascending aorta. (*C*) Abdominal aortogram showing double-barrelled aorta with origin of right renal artery from one channel, and that of the visceral arteries from the other channel. (Previously published.[19])

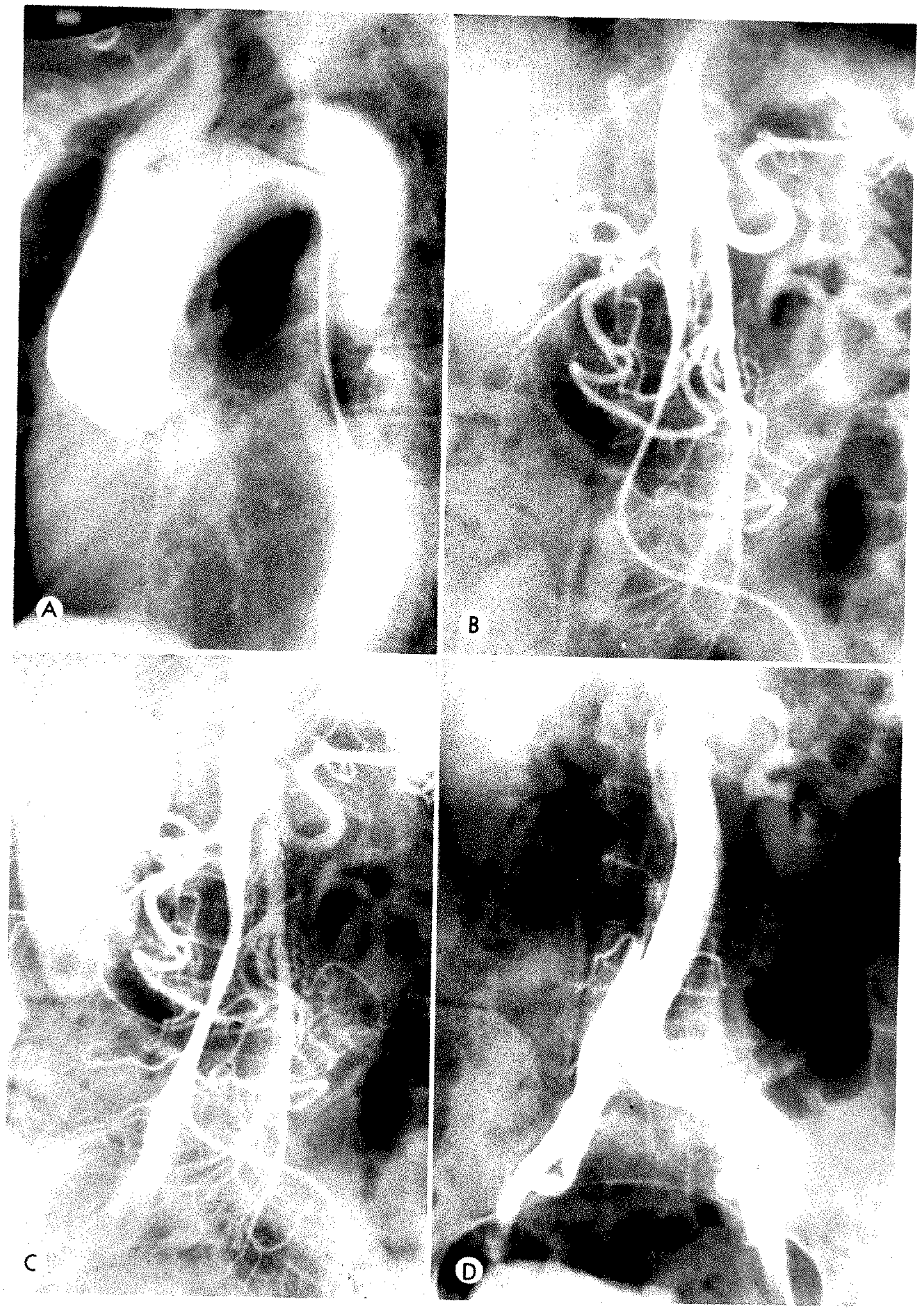


FIG. 9. (*A*) Left oblique thoracic aortogram showing large dissection of ascending aorta. Both channels are well opacified; however, the sinuses of Valsalva are not seen because the injection was made into the false lumen of the ascending aorta. (*B*) Abdominal aortogram (1 sec.) showing filling of a narrow true lumen, which opacifies the celiac axis, superior mesenteric, and right renal arteries. (*C*) Abdominal aortogram (2 sec.) showing further filling of true channel and some of its branches. (*D*) Abdominal aortogram with injection into false channel adjacent to re-entry point at aortic bifurcation. Note filling of a wide false lumen from which the left renal artery is opacified.

were noted in 2 instances and were due to persistent shallow communications between the true and false channels.[8] These resemble the appearance of gastric ulcers. The "crater" in dissecting aneurysms is due to extravasated contrast material in the thrombosed false channels and the linear lucencies akin to Hampton's lines represent the wall between the true and false channels (Fig. 7, *A* and *B*). This finding, in the presence of a grossly thrombosed false channel, is an important diagnostic sign of dissection.

When the thoracic aortic channel is narrowed, and the adjacent density is suspected of being a thrombosed false lumen, visualization of the abdominal aorta may establish the definitive diagnosis of dissecting aneurysm. In neoplastic disease adjacent to the aorta, a considerable amount of soft tissue density may sometimes be seen

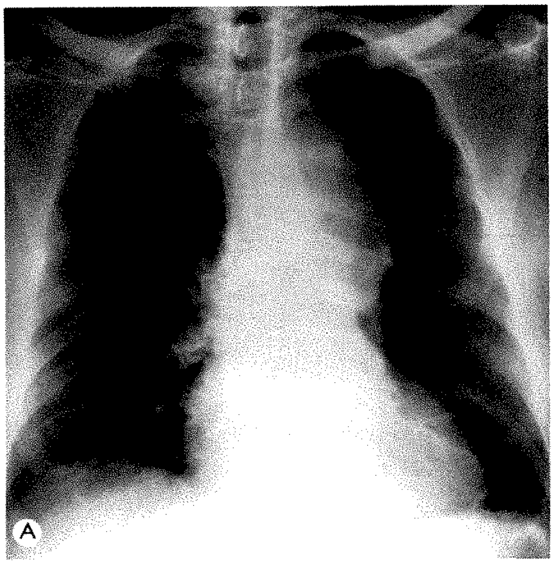


Fig. 10. (*A*) Conventional frontal teleroentgenogram of the chest showing an enlarged descending thoracic aorta.

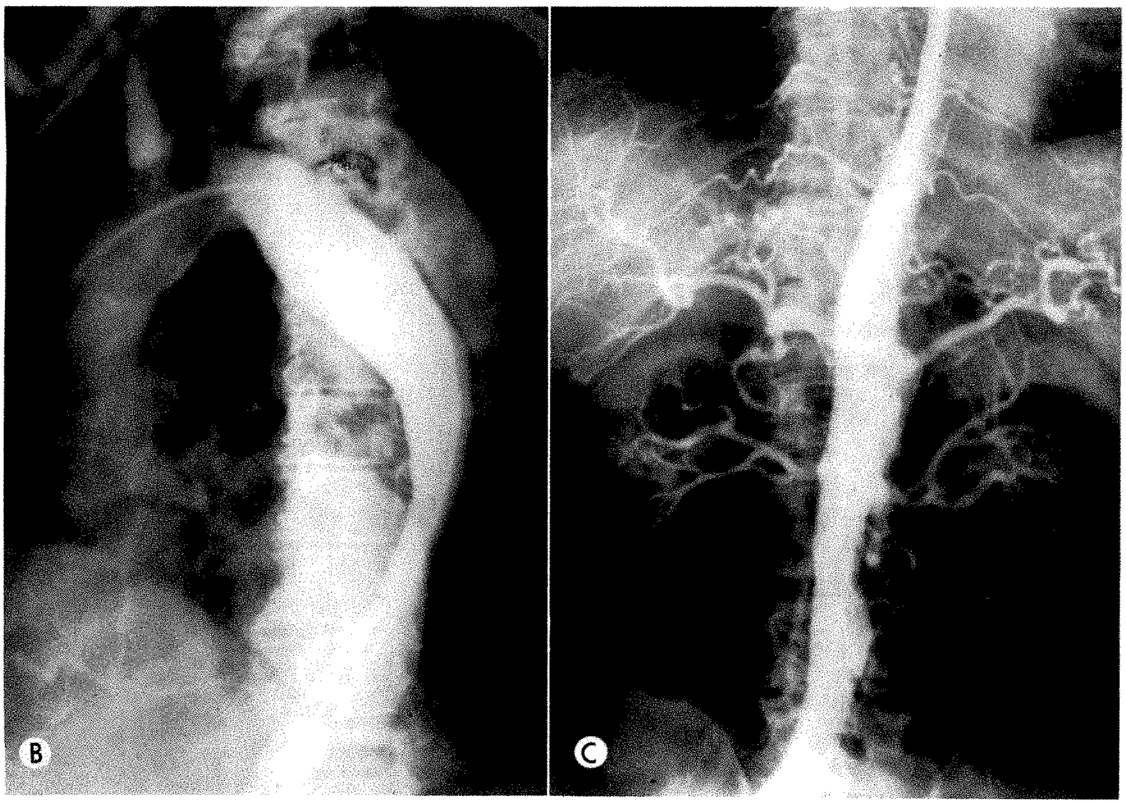


Fig. 10. (*B*) Oblique thoracic aortogram revealing double lumen aorta with dissection beginning distal to left subclavian artery. (*C*) Abdominal aortogram showing narrowed and distorted true lumen without visualization of false channel.

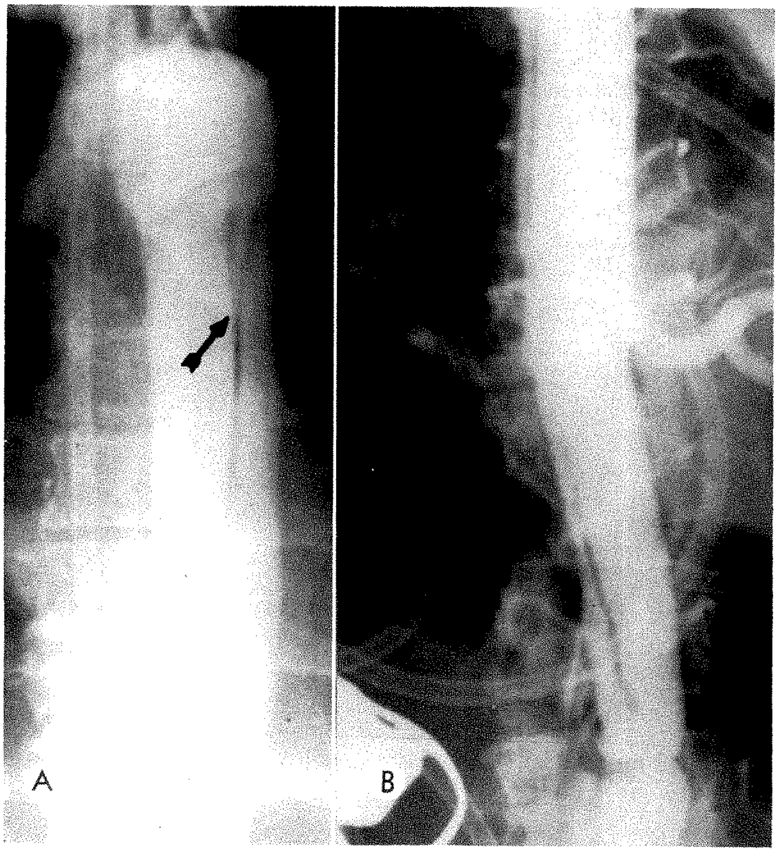


Fig. 11. (*A*) Frontal thoracic aortogram revealing double lumen aorta with lucent wall between the channels. Note the apparent splitting of the wall due to the circumferential nature of the dissection (arrow). (*B*) Abdominal aortogram showing double lumen of the aortic dissection.

beyond the opacified aortic lumen, and an erroneous diagnosis of dissection with a thrombosed false channel be made. In 4 of 6 cases where the false channel in the thoracic aorta was thrombosed and the abdominal aorta was examined, two abdominal aortic channels were revealed, often with the visceral blood supply originating partly from each (Fig. 3, *B* and *C*; 8*C*; and 9, *B-D*). Indeed, in these cases, although anatomically there is a true and false channel, this would not seem to be of physiologic significance. Where injections were made alternately first into one channel, then into the other, part of the visceral blood supply was derived either from one or the other channel (Fig. 3, *B* and *C*; 8*C*; and 9, *B-D*).

Figure 12*A* shows an apparently normal abdominal aorta in the frontal projection without extension of dissection from the thorax. The lateral projection, however, revealed two channels, with the false channel located posteriorly and of greater width than the compressed anterior lumen (Fig. 12*B*). Therefore, the abdominal aorta should be examined routinely and in more than one projection, especially if the frontal view fails to demonstrate the full extent of the dissection.

SUMMARY AND CONCLUSIONS

The diagnosis of dissecting aneurysm was established in 18 patients employing the technique of percutaneous catheter aortography. This method has proven safe and without complication. Transfemoral or transaxillary arterial puncture, or both, were used, depending upon the presence and quality of peripheral pulses, and need

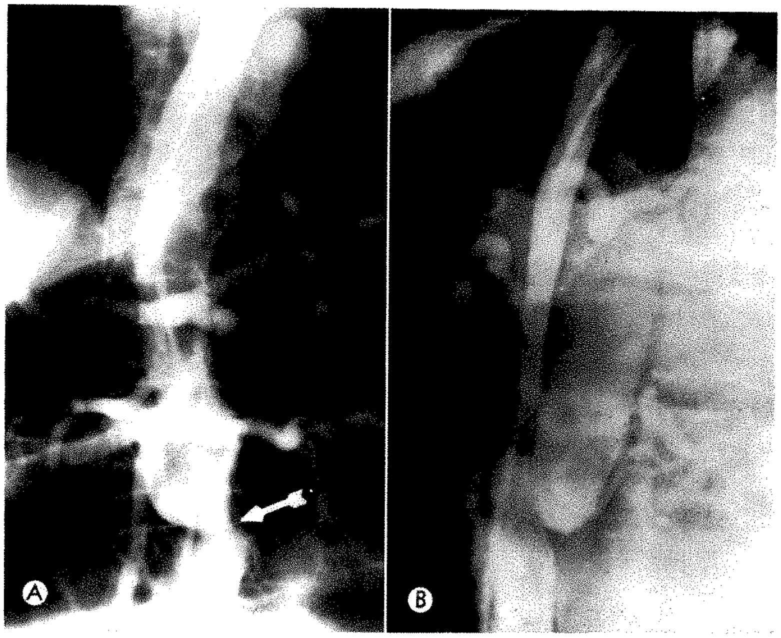


Fig. 12. (*A*) Frontal thoracoabdominal aortogram showing opacification of the false channel in the thorax while the abdominal aorta (true channel) appears to be of normal width except for an area of stenosis distally (arrow). (*B*) Lateral abdominal aortogram showing the true channel compressed anteriorly by the wide false lumen. Re-entry point is at site of "stenosis." (Courtesy of Dr. G. Törnell, Thoraxklinik, Karolinska Sjukhuset, Stockholm, Sweden.)

to secure complete evaluation of both the thoracic and abdominal aorta.

The definitive diagnosis of dissecting aneurysm requires opacification of a double-lumen aorta with visualization of the lucent wall between the two channels. Complete and incomplete opacification of the false channel was encountered, depending upon patency of the false channel. The various patterns of incomplete thrombosis of the false channel in the thorax, such as ulcer-like projections into the false channel and localized extravasation of contrast material at sites of intimal tear are described and illustrated. When complete thrombosis of the false thoracic lumen is found, visualization of two distinct channels in the abdominal aorta confirms the diagnosis. Hence, evaluation of the full extent of the dissection is incomplete without the examination of the abdominal aorta in one or more projections. Suggestive signs of aortic dissection are narrowing of the opacified channel and incomplete filling of arteries to clinically viable viscera.

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Thanks are due to Dr. Robin C. Watson who performed the aortographies on many of these patients.

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RETROGRADE CATHETER AORTOGRAPHY IN DISSECTING AORTIC ANEURYSMS*

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PRECISE definition of the limits of dissecting aneurysms is essential prior to surgery. Recent reports of complications arising from retrograde catheter aortography in this condition have discouraged many investigators from using this technique. Our experience in a large series of cases examined by this method has been without serious complications. In our hands, the excellent contrast obtained by this technique surpasses that of other procedures and clearly demonstrates the extent of the dissection.

TECHNIQUE

In 1948, Radner introduced a new method of thoracic aortography through a catheter placed in the radial artery and advanced by way of the brachial, axillary and subclavian arteries into the aorta. Later, Broden, Hanson, Karnell and Jonsson thoroughly explored the value of this method. Pierce modified the catheter technique by the introduction of percutaneous femoral artery puncture and catheter insertion through the needle.[1]

In 1953, Seldinger[17] published his famous technique which has been adopted as a standard for retrograde femoral aortography. Various modifications of his technique have been developed using an Ödman polyethylene catheter.

For investigation of dissecting aortic aneurysms, we prefer this retrograde femoral approach. The Seldinger technique is employed using a No. 7 Gensini catheter. We attempt to pass the tip of the catheter through the true lumen into the aortic root for the initial injection. However, if the catheter passes through the false channel we have not hesitated to inject the contrast medium at the origin of the intimal tear. Forty cubic centimeters of renovist is used, employing a Cordis injector under 750 pounds pressure at the injector head. Films are exposed in the right posterior oblique position with a cut-film Schönander cassette changer at 4 frames per second. The catheter is frequently re-positioned for a second injection, if both channels have not been delineated, or the re-entry sites of the dissection are not clearly outlined. Proper surgical correction depends upon the definition of the precise point of intimal tear (Fig. 1–3). Dissection into a triple lumen has been demonstrated in 1 case.

COMPLICATIONS

In 1957, Abrams published a survey in respect to the hazards of retrograde thoracic aortography.[2] Evaluating 1,706 thoracic aortographies, 29 deaths were recorded; dissection occurred in only 1 case. McAfee[14] published a national survey, including evaluation of 13,207 abdominal aortographies. In his series, 37 deaths and 98 serious complications occurred. The complication rate was 1.02 per cent and the mortality rate 0.28 per cent. In this series, 375 retrograde aortographies were performed with 141 cut-downs, and with 234 percutaneous injections. Two deaths were reported as a complication of dissecting aneurysm.

In reviewing a series from 1953 to 1959, Gudbjerg and Christensen[6] found that among 451 examinations, intramural position of contrast material was demonstrated in 36 cases out of 419. This shows a 9 per cent incidence which is compatible with the figures reported by other investigators.[6,7,13,15,16] In their respective series, these investigators emphasize the pre-

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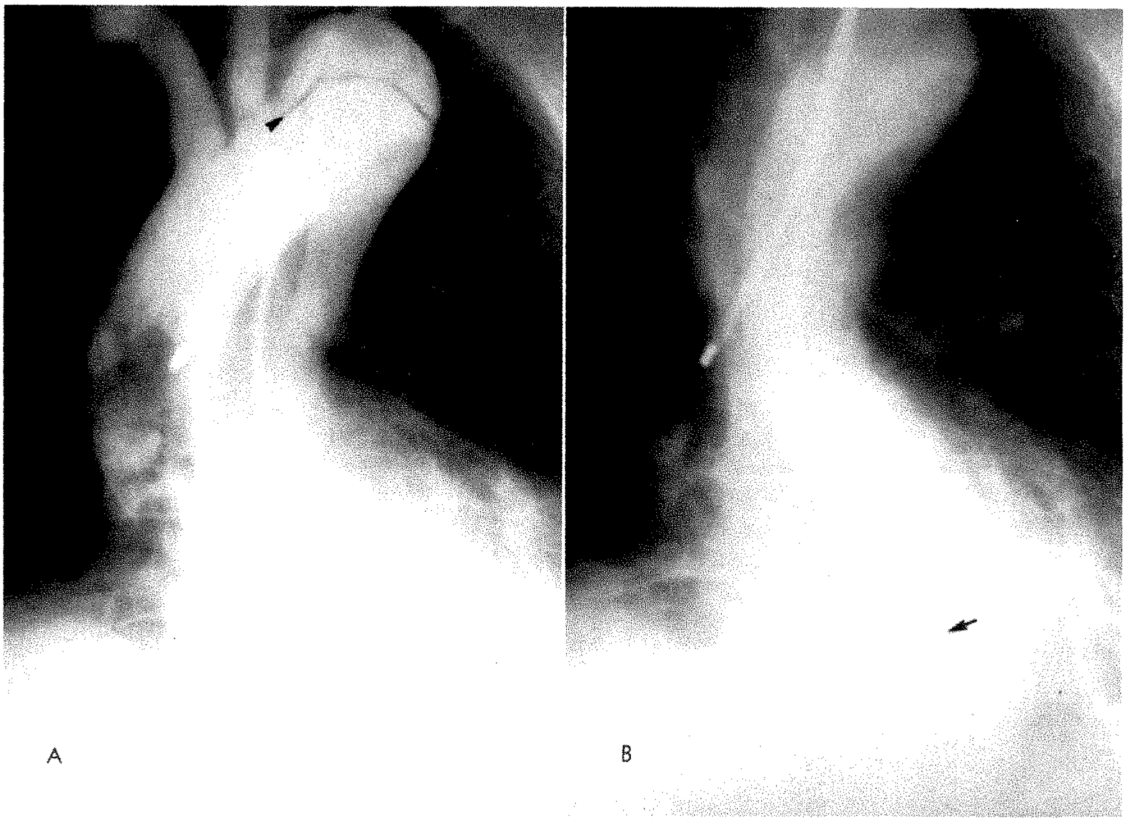

Fig. 1. The evening prior to admission, this 46 year old male developed excruciating chest pain radiating to the back. This was followed by paralysis of the right leg. (*A*) Injection was made into the ascending aorta. The radiolucent line is the site of tear in the aortic arch adjacent to the left subclavian artery. There is compression of the true lumen in the descending aorta. (*B*) The dissection extends into the abdominal aorta. The catheter passes from the false lumen into the true lumen in the lower portion of the descending thoracic aorta (arrow).

existing signs of arterial wall disease. In 27 out of the 36 patients there was difficulty in performing the catheterization and advancing the catheter. Templeton *et al.*[21] reported 1 case of dissection with a retrograde brachial study and felt that the cause of the dissection was secondary to the catheter. However, pre-existing arterial wall disease was observed in this case. Williams and Johnson[22] reported aortic dissection after femoral cannulization in a retrograde fashion. In their case cystic medial necrosis was present, which is one of the underlying causes of dissection. Tawakkol and Bacos[20] are not enthusiastic in advocating this procedure. They recommend the direct percutaneous non-catheter brachial angiography, popularized by Marshall and Ling, to demonstrate aortic abnormalities, and to evaluate the thoracic aorta.

Because of reported complications arising from retrograde femoral catheterization, percutaneous needle arteriography is widely used. Other investigators recommend venous arteriography.[3,9,18,19]

With a retrograde brachial catheterization, it is commonly necessary to do additional retrograde catheterization from one or both femoral arteries in order to demonstrate the distal extent of the dissection and the details of any re-entry aperture.[4] Thus, we prefer to use the femoral approach initially. In over 75 cases examined for dissecting aneurysms, we have had no difficulty in passing the catheter from the femoral artery. Entry into the dissected

sac frequently occurred, but never resulted in a complication. We do not consider this a hazard, and often knowingly inject the contrast medium into the false channel. We then have the opportunity to withdraw the catheter into the lower descending thoracic or abdominal aorta and re-inject to outline the site of possible re-entry.

DISCUSSION

Within recent years the surgical approach to dissecting aneurysms of the aorta has been from palliation to complete correction and restoration of physiologic and mechanical normality. Seventy-five per cent of untreated cases will have a fatal termination within 2 months, but relatively few patients die within the first 24 hours. Twenty-five per cent of patients will survive 2 months or more, following the acute process.[10–12] Thus, in most patients there is adequate time for diagnostic studies and surgical procedures. The findings on plain roentgenograms and laminagrams were discussed by Eyler and Clark[5] in 1965. The accuracy of contrast angiography has made possible the correct premortem diagnosis in the great majority of cases. Not only must the diagnosis be made, but the precise definitions of the dissection are essential for proper surgical management.[10] It is our belief that this is best accomplished by retrograde catheter aortography. The success obtained by others with venous angiography and percutaneous retrograde arteriography has not been duplicated at our institution. Percutaneous femoral catheterization by a modified Seldinger technique is our method of choice. In less than 5 per cent of cases has it been necessary to resort to axillary catheterization. This most often occurred in elderly patients with advanced arteriosclerosis. In over 200 suspected cases performed through the femoral approach, we have had no serious complication despite duplicate injections at different sites in many patients. Passing the catheter into the false lumen has never presented a major problem. The clear demonstration of the limits of double and triple lumen dissections has guided the surgical decisions. Patients in whom the dissection arises distal to the left subclavian artery have, for some time, been amenable to total correction. With the development of safe techniques to approach the ascending aorta and aortic valve, total correction may now be offered to the group of patients having dissections proximal to the aortic arch. Without surgery, the mortality rate is high. In a certain selected series of patients, immediate surgery following adequate aortography can produce a success rate of 70 per cent.

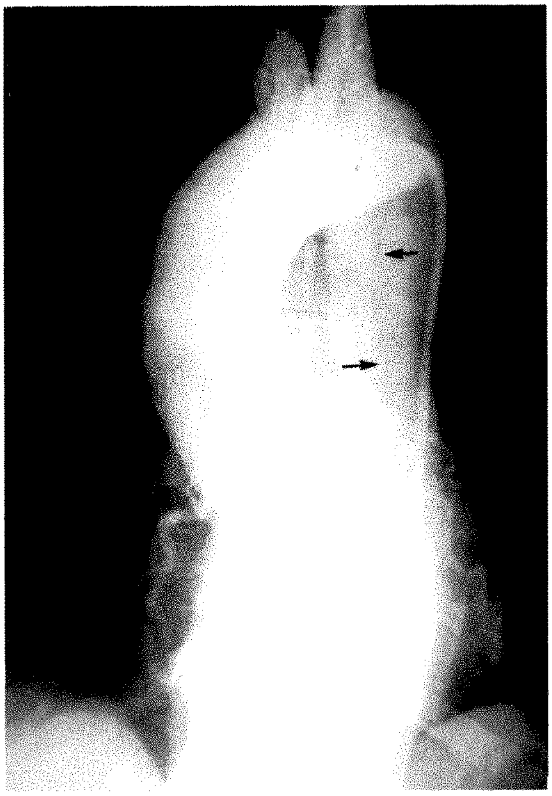

Fig. 2. The catheter passes through the false lumen throughout. The dissection begins 1 cm. above the coronary arteries and extends through the descending thoracic aorta into the abdominal aorta. The vertical radiolucent line (arrows) defines the separation between the false and true channels.

SUMMARY

Retrograde femoral aortography is the definitive diagnostic method of choice for dissecting aneurysms of the aorta.

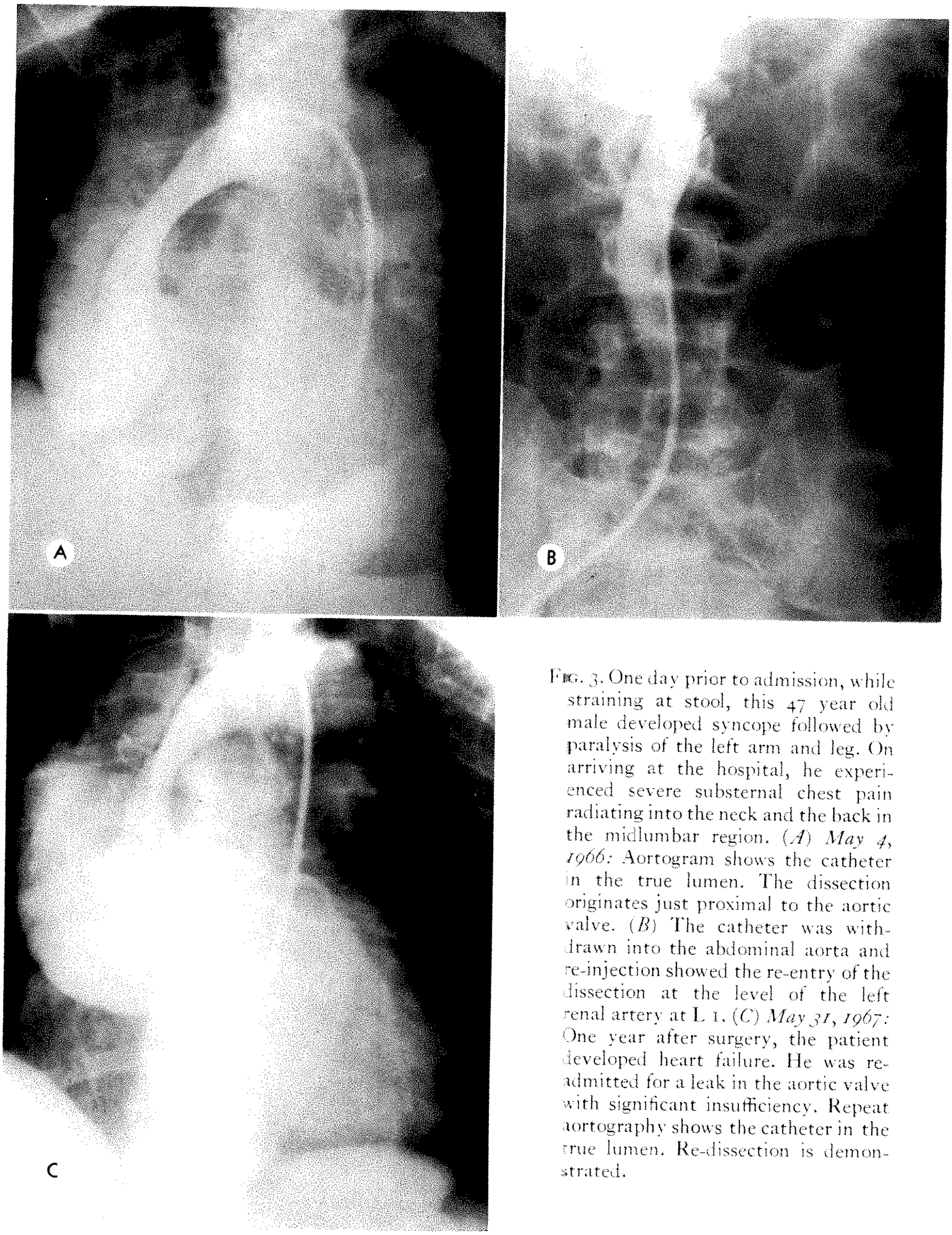

Fig. 3. One day prior to admission, while straining at stool, this 47 year old male developed syncope followed by paralysis of the left arm and leg. On arriving at the hospital, he experienced severe substernal chest pain radiating into the neck and the back in the midlumbar region. (*A*) *May 4, 1966:* Aortogram shows the catheter in the true lumen. The dissection originates just proximal to the aortic valve. (*B*) The catheter was withdrawn into the abdominal aorta and re-injection showed the re-entry of the dissection at the level of the left renal artery at L 1. (*C*) *May 31, 1967:* One year after surgery, the patient developed heart failure. He was readmitted for a leak in the aortic valve with significant insufficiency. Repeat aortography shows the catheter in the true lumen. Re-dissection is demonstrated.

Sites of intimal tear and re-entry may be clearly demonstrated.

Injections into both true and false lumens may be made.

Our investigations with this method in a large series of cases have been without serious complications.

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MYCOTIC ANEURYSMS*

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ALTHOUGH Koch is credited with the original pathologic description of a mycotic aneurysm in a patient with bacterial endocarditis, the term was introduced by Osler[22] in 1885 to denote aneurysms resulting from an infectious process involving the arterial wall. Since the initial usage of the term, a modified nomenclature has appeared in the literature. "Primary mycotic aneurysm," coined by Crane,[10] refers to those infectious aneurysms unassociated with a demonstrable intravascular inflammatory process such as bacterial endocarditis or with spread of infection by contiguity from an adjacent suppurative process.[27] This is in distinction to the far more common "secondary mycotic aneurysms" associated with a known source of infection. "Cryptogenic mycotic aneurysms"[5,6] include those which arise in the absence of any obvious source of infection. Mycotic aneurysms account for approximately 2.5 per cent of all aneurysms.[24]

Prior to the advent of antibiotics, mycotic aneurysms were almost uniformly fatal if one of the larger arteries was involved, even when the diagnosis was suggested preoperatively. With intense antibiotic therapy and additional surgical experience, an increasing number of patients have survived. The lesion must first be diagnosed, however, before proper therapy can be instituted. Unfortunately, the most lethal locations, such as the aorta, frequently present with minimal signs and symptoms at an early stage, whereas the least disastrous, the peripheral arteries, are more readily recognized. A high index of suspicion followed by immediate angiographic investigation is essential, for the disintegration of the arterial wall progresses rapidly and any hesitation may prove fatal.

It is the purpose of this paper to present and review several cases of mycotic aneurysms, 2 terminating fatally, with the expectation that an increased awareness of the lesion will result in an earlier diagnosis and a better prognosis.

REPORT OF CASES

CASE I. J. D., a 55 year old white male, was hospitalized with the chief complaint of 6 days of progressively increasing pain in the left groin which recently had become unbearable. Associated findings included swelling of the thigh and a spiking fever which had not been apparent initially.

Physical examination demonstrated pitting edema, plethora and venous engorgement of the left thigh. A tender, pulsatile mass 7 cm. in diameter was palpable in the left inguinal area. The popliteal and dorsalis pedis pulses were present bilaterally although significantly reduced on the left. A Grade II systolic murmur was heard best at the cardiac apex.

The patient continued to spike high temperatures and had an elevated white blood cell count. Blood and stool specimens grew Salmonella typhimurium which was sensitive to chloromycetin and neomycin. An abdominal roentgenogram disclosed prominent calcification of the aorta and iliac arteries but no evidence of aneurysm formation. A retrograde aortogram demonstrated the markedly atherosclerotic aorta and iliac arteries; in addition, a smooth-walled, saccular aneurysm was opacified. It measured 5.5 cm.×6.5 cm. and originated at the bifurcation of the common femoral artery (Fig. 1). A venogram disclosed complete obstruction of the common femoral vein, presumably secondary to pressure from the aneurysm with prominent collateral venous circulation about the hip.

Six days following his admission, the left

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femoral artery was surgically explored and a 6 cm.×8 cm. false aneurysm was identified arising from the posterior aspect of the common femoral artery. The aneurysm was excised and the wound debrided. A saphenous vein by-pass graft was utilized to preserve peripheral blood flow; postoperatively the distal pulsations were adequate. The incision was left open for a delayed primary closure. The pathologic specimen demonstrated arteriosclerotic intima, organizing thrombus and acute and chronic inflammation of the surrounding tissue. A culture of the aneurysm yielded Salmonella typhimurium.

The postoperative course was uneventful with the exception of incomplete healing of the incision which drained seropurulent material containing Salmonella typhimurium. Salmonella was isolated from the stool but multiple blood cultures were sterile. The patient was discharged to be followed in a hospital near his home.

Nine days later, a sudden brisk hemorrhage occurred in the region of the saphenous vein graft. Exposure of the left femoral artery revealed the proximal and distal anastomosis to be intact but aspiration of a small abscess adjacent to the proximal portion of the graft resulted in spontaneous rupture and bleeding, controlled by a common femoral artery ligature proximal to the venous graft. Culture of the wound again produced a heavy growth of Salmonella typhimurium. Because of arterial insufficiency and the production of a dry gangrene of the first, second and third toes, the patient had a supracondylar amputation. The groin and stump healed well postoperatively and the patient was discharged. The follow-up examination 2 years later was unremarkable.

Fig. 1. Case i. A false saccular aneurysm of the common femoral artery, overlying the femoral head, is opacified by retrograde aortography. Salmonella typhimurium was cultured from the aneurysm.

Case ii. G. S., a 21 year old male, entered the hospital because of chills, fever, and painful and numb feet. These symptoms developed 3 weeks prior to admission and had responded temporarily to terramycin and other antibiotics. Past history was otherwise unremarkable.

Physical examination revealed an acutely ill, pale, patient with conjunctival petechiae, splinter hemorrhages of the fingernails and toenails, and swelling of the ankles and feet. There was a Grade iii harsh apical systolic murmur but no cardiomegaly. Liver and spleen were tender and slightly enlarged. The initial red blood cell count was 2.5 million with 8,100 white blood cells but the latter increased to 21,000. Multiple blood cultures, including a bone marrow specimen, were negative prior to and following discontinuance of antibiotic therapy.

Following the presumptive diagnosis of subacute bacterial endocarditis superimposed upon a rheumatic mitral valvular lesion, the patient was placed on various regimens of antibiotic therapy but the spiking febrile response continued. Six weeks later, there was a sudden onset of severe mid-abdominal pain and mesenteric embolism was considered. A mass in the region of the left common iliac artery was first noticed 1 month thereafter and within 2 weeks had increased significantly in size and was associated with a murmur. The peripheral pulses of the left leg were diminished. An intravenous and retrograde pyelogram demonstrated lateral displacement of the left ureter at the L4 level (Fig. 2). A translumbar aortogram opacified a large saccular aneurysm of the distal abdominal aorta which displaced

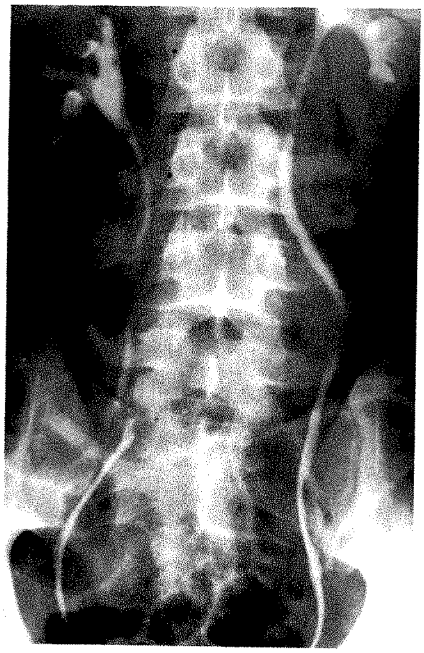

Fig. 2. Case II. Retrograde pyelogram reveals lateral displacement of the middle third of the left ureter by a retroperitoneal mass.

and partially obstructed the left ureter (Fig. 3).

At operation, it was impossible to excise the aneurysm which was then by-passed with a homograft. Following surgery, pulsations to the lower extremities were adequate but 2 days later were not palpable. The circulation appeared adequate otherwise and no attempt was made to revise the graft at that time. Six weeks after surgery the patient expired. Autopsy revealed a perforation through the homograft and rheumatic vegetations involving the mitral valve. Death was due to intra-abdominal and retroperitoneal hemorrhage from a rupture of the homograft.

Case III. N. S., a 54 year old white male, was hospitalized with a 4 week history of dyspnea, fever and night sweats. Five days prior to admission the patient noted the onset of right upper quadrant and mid-back pain which was accentuated by deep inspiration. Two days before hospitalization he expectorated blood streaked sputum. The past history was noncontributory with the exception of a partial right upper lobectomy for tuberculosis 8 years previously. Positive physical findings were restricted to an enlarged liver and rales, rhonchi, and wheezes at the right lung base.

In the laboratory work-up, Salmonella typhimurium, sensitive to chloromycetin, was isolated from the sputum, stool and blood. Following antibiotic therapy the fever and abdominal pain disappeared but the production of bloody sputum continued. A chest roentgenogram 1 week after admission revealed infiltration at the right lung base, pleural reaction, and a soft tissue mass in the right cardiophrenic angle (Fig. 4, *A* and *B*). A chest roentgenogram 4 weeks later demonstrated marked enlargement of the soft tissue mass in the right cardiophrenic angle with anterior displacement of the distal esophagus (Fig. 5, *A* and *B*). With the presumptive diagnosis of mediastinal abscess, a limited thoracotomy was performed. Aspiration of blood from a mass encountered during the exploration resulted in the new diagnosis of mycotic aneurysm of the descending thoracic aorta. No further definitive surgery was performed and an aortogram the next day demonstrated a large saccular aneurysm arising at the level of the diaphragm, measuring 6 cm. in diameter and compressing the aorta (Fig. 6). Two days later the aneurysm was resected and a teflon graft inserted. The aneurysm was 15 cm. in diameter with extremely thin walls and posteriorly the wall was virtually nonexistent, being formed by the vertebral bodies. Postoperatively, the patient survived two cardiac

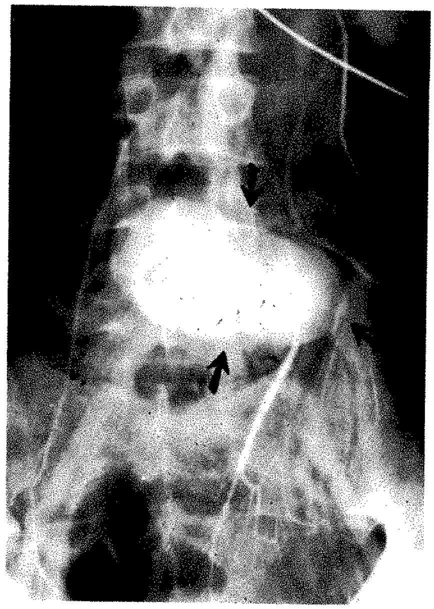

Fig. 3. Case II. Translumbar aortogram demonstrates a large saccular aneurysm arising at the bifurcation of the aorta and responsible for the lateral deviation of the left ureter.

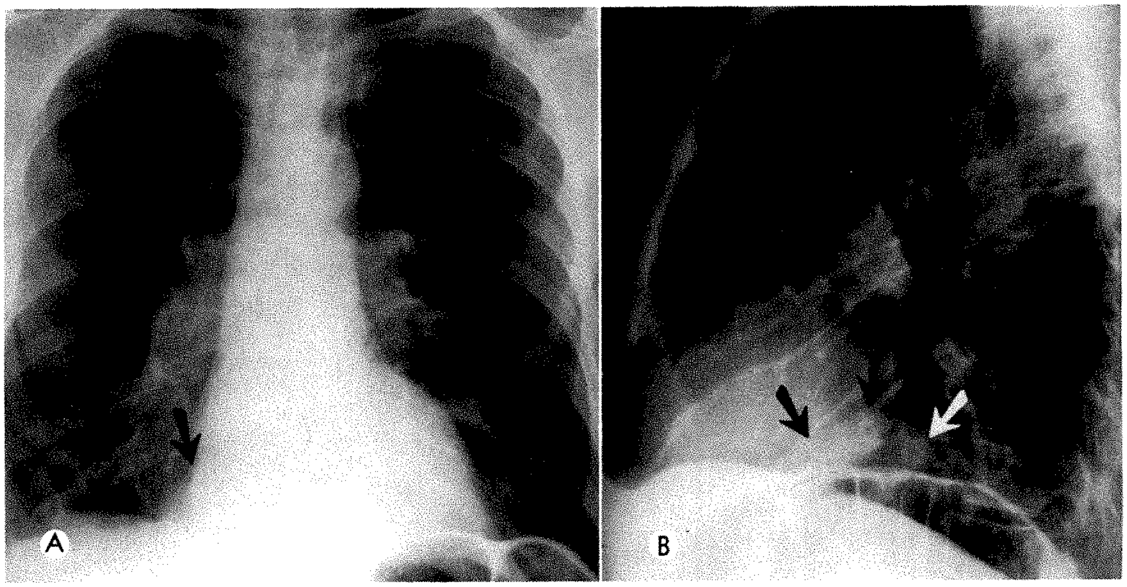

Fig. 4. Case III. (*A*) Posteroanterior and (*B*) lateral chest roentgenograms reveal infiltration and pleural reaction at base of right lung, and a soft tissue mass in the right cardiophrenic angle (arrows).

arrests but continuing hypotension necessitated a second operation during which 1,000 ml. of clotted blood was removed from the left pleural space, but the source of bleeding was not identified. The patient never recovered consciousness and expired 10 days later. Pathologic examination of the surgical specimen revealed intimal atherosclerosis, necrosis of the media and adventitia and extensive fibrosis of the aortic wall. The unorganized adventitial blood clot appeared to be in continuity with the aortic lumen. Salmonella typhimurium was

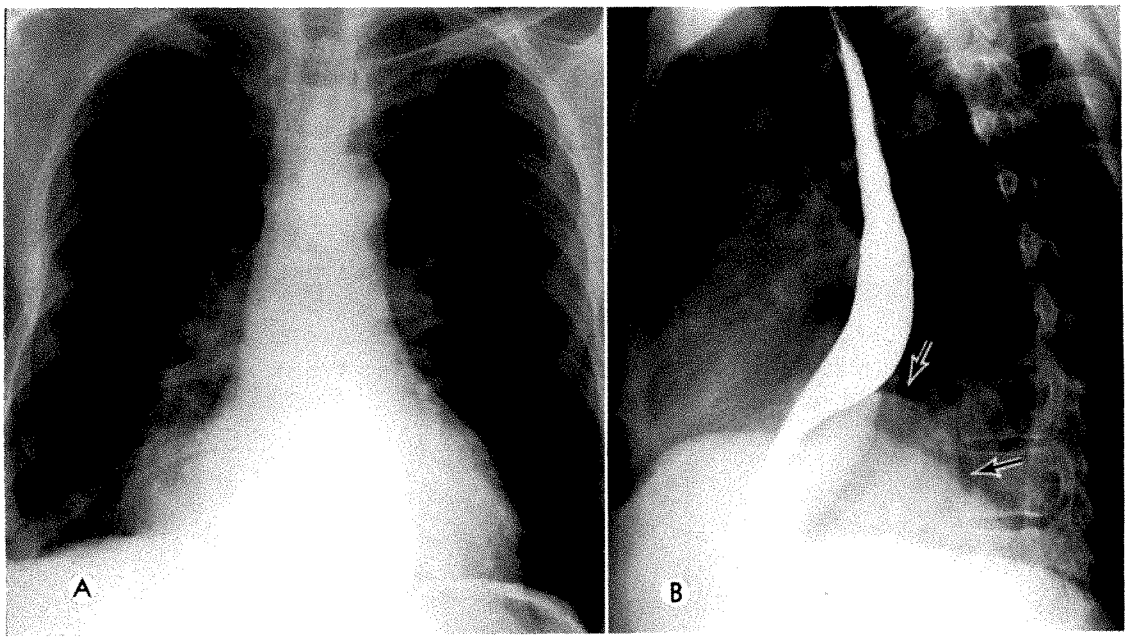

Fig. 5. Case III. (*A*) Posteroanterior and (*B*) lateral chest roentgenograms, with barium swallow 4 weeks later demonstrate marked progression in size of the soft tissue mass in the right cardiophrenic angle and anterior deviation of the distal esophagus.

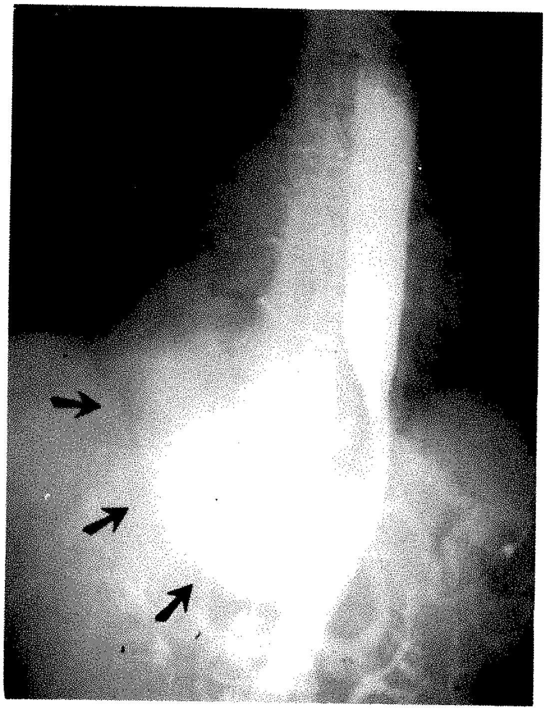

Fig. 6. Case iii. Thoracic aortography delineates a large saccular aneurysm originating from and compressing the descending thoracic aorta at the level of the diaphragm.

cultured from the wall of the aneurysm.

At autopsy, examination of the heart failed to reveal any evidence of bacterial endocarditis. The proximal and distal anastomotic sites were intact as was the teflon graft. Postmortem blood cultures were sterile, but the peritoneal fluid, aortic wall and left para-aortic hematoma grew out Pseudomonas.

DISCUSSION

PATHOLOGY

Development of a mycotic aneurysm requires a source of infection and, usually, damage to the vascular wall by atherosclerosis, cystic medial necrosis, syphilitic aortitis, external trauma, or congenital defects such as coarctation[31] or hypoplasia of the aorta. The intact intima is extremely resistant to infection although in bacterial endocarditis an infected embolus may wedge in a normal vascular tree at a bifurcation, a normal but sharp turn in the vessel, or at a site of rapid tapering.

The arterial wall may be affected through a variety of routes. Embolization from bacterial endocarditis is the most frequently reported factor.[1,18,35] The infection may spread from an adjacent area, either intravascular or extravascular. Tuberculous involvement is usually secondary to extension by contiguity,[15,23] although hematogenous spread and embolic deposition have been reported.[23] This mechanism may also be applicable when the sinus of Valsalva or ascending aorta are involved in patients with bacterial endocarditis of the aortic cusps. In the preceding instances, the aorta may be normal or diseased. In septicemia bacteria lodge on the abnormal intima or in the vasa vasorum. In the absence of endocarditis, the most common causes of bacteremia are lung and bone infections; other sources include infectious arthritis, esophagitis, urethritis, cellulitis of the soft tissues and cystitis. In many, particularly with Salmonella, the origin of the bacteria is never determined. Lymphogenous extension via the perivascular lymphatics infrequently is responsible for an arteritis.

Any artery may be affected by mycotic aneurysms; in a significant number of cases they are multiple. Several authors[24,27,35] note the predominant involvement of the thoracic aorta, primarily the ascending aorta and arch. Lewis and Schrager[18] list the superior mesenteric artery as the most common site. The intracranial vessels, primarily the middle cerebral artery, are next in frequency followed by the large arteries of the extremities, particularly the femoral and brachial. Intra-abdominally, the hepatic and splenic arteries may be diseased. Tuberculosis involves primarily the abdominal aorta by extension from caseating lymph nodes.

With the development of an arteritis, the pathology usually progresses in one of two directions, depending primarily upon the virulence of the organism. A rapid disintegration of the wall with rupture may ensue without any dilatation. Primary mycotic aneurysms frequently are of this type. If a large vessel is involved, the artery bleeds freely into the pericardial, pleural or peri-

toneal space or may rupture into the bronchial tree, lung or gastrointestinal viscera.[7,18,24,25,26,37] When a peripheral artery perforates, a false aneurysm may develop with the wall composed of compressed perivascular tissues with or without an intact adventitia. Occasionally, a false aneurysm develops elsewhere as occurred in Case III. False aneurysms may eventually rupture but thrombosis with complete healing does occur. When the destruction proceeds slowly, as is often true with mycotic aneurysms secondary to bacterial endocarditis, dilatation may occur first with the formation of a true aneurysm. Eventually, these may rupture, but some never do and complete healing may occur.

Grossly, mycotic aneurysms vary greatly in appearance. Often millet seed in size, they are rarely larger than a walnut, even in the larger arteries, except where a false aneurysm develops.

Histologically, there is a loss of intima, destruction of elastic tissue, particularly the internal elastic lamina, and acute or subacute periarteritis and mesarteritis. The muscularis may be partially or totally destroyed as is true of the adventitia. Usually it is possible to differentiate mycotic from other types of aneurysms by microscopy.

Nonhemolytic streptococci were identified in the majority of mycotic aneurysms secondary to subacute bacterial endocarditis but staphylococci, pneumococci, bacillus influenzae, salmonella, gonococcus, and other organisms have also been cultured.[11,24,27,35]

Salmonellosis is receiving increased recognition as an important cause of mycotic aneurysm. Two of the three reported cases of mycotic aneurysm in this article were secondary to Salmonella typhimurium.

CLINICAL FINDINGS

Typically, mycotic aneurysms have an insidious onset with nonspecific symptoms such as malaise, fever, chills, and increased weakness. Consequently, rupture as early as 1 to 2 weeks following onset of symptoms often occurs prior to diagnosis. When localized to an intracranial, intrathoracic, or intra-abdominal artery the diagnosis may not be established until autopsy. Peripheral arteries situated superficially offer the best opportunity for early recognition. Here the pain, swelling, and tenderness may be erroneously diagnosed initially as thrombophlebitis, but the development of a pulsating mass, representing a true or false aneurysm, suggests the lesion. Absent pulsations and circulatory impairment are often apparent distal to the aneurysm although gangrene is uncommon. Mycotic aneurysm of the abdominal aorta may produce severe epigastric or lumbar pain, urologic complaints and a vascular or neurogenic type of discomfort of the lower extremities but the diagnosis depends upon demonstrating a pulsating abdominal mass, thrill, or bruit. Severe epigastric pain occurs with superior mesenteric artery aneurysms. These aneurysms are palpated inferior and to the right of the umbilicus and may be displaced spontaneously or manually about the abdomen. Hepatic artery aneurysms may present with pain over the liver, jaundice, and bleeding into the gastrointestinal tract. With intracranial involvement, the neurological examination suggests intracerebral hemorrhage or embolism. A past history of endocarditis or a known active infection is helpful. It is important to document the presence of a septic process by stool or blood cultures. Leaking aneurysms result in a leukocytosis up to 20,000, but a temperature elevation suggests bacteremia.

ROENTGENOGRAPHIC FINDINGS

Mycotic aneurysms have no characteristic roentgenographic features that distinguish them from other types of aneurysms other than their sudden appearance, rapid progression in size, and occasional uncommon localization. Aneurysms situated peripherally in the middle cerebral artery are invariably mycotic,[8] while those involving the superior mesenteric artery have a high incidence of mycotic aneurysms.[12] Whether a true or false an-

eurysm, they tend to be saccular but this configuration is also found with luetic, arteriosclerotic, traumatic and congenital aneurysms.

Luetic aneurysms situated in the ascending aorta and arch are frequently associated with dilatation of the sinuses of Valsalva and aortic insufficiency. Traumatic aneurysms may appear suddenly and progress rapidly but are characterized by a predilection for fixed portions of the aorta, namely, the aorta distal to the valve and at the origin of the left subclavian artery. Arteriosclerotic aneurysms may be distinguished by their older age incidence and other features of atherosclerosis. Atherosclerotic aneurysms may become secondarily infected during a bacteremia.[17,34] Saccular aneurysms of an extremity, particularly the femoral triangle and popliteal fossa, are most commonly arteriosclerotic, occasionally traumatic, but when infectious, their inflammatory nature is obvious.

Thoracic and abdominal aortic aneurysms may be suspected on routine roentgenographic examinations. Occasionally, the etiology of the mass may be obscure; in Case III, for example, it was initially considered a mediastinal abscess. A similar case was reported by Yanoff *et al.*[38] Angiographic studies are required to delineate intracranial and visceral artery aneurysms as well as to substantiate the diagnosis in the thoracic or abdominal aorta.

PROGNOSIS AND TREATMENT

When visceral arteries are affected, the prognosis is grave because the absence of specific clinical findings precludes early diagnosis. With peripheral artery aneurysms, the outcome is more favorable, since their superficial location enables an earlier diagnosis. Rarely, spontaneous cures due to thrombosis have been reported.[20,21] Even when recognized early, surgical correction may not be possible because of the extensive infection and necrosis which prevent adequate healing at the anastomotic site. The longer the delay in instituting proper therapy, the more extensive the infected and devitalized tissue and the less the chance of a favorable outcome.

The aim of therapy is twofold: (1) eradication of the underlying infection; and (2) removal of the aneurysmal sac and reconstruction of the artery, when necessary to maintain continuity of blood flow.[36] Appropriate antibiotic therapy preoperatively will render the blood stream sterile in the majority of cases, but unless the aneurysmal sac is extirpated, it will serve as a persistent source of reinfection.

Surgical correction is more successful when repairing smaller vascular structures like the femoral, brachial, or superior mesenteric arteries than with larger arteries such as the thoracic or abdominal aorta. The best results are achieved when only a simple ligation of the blood vessel and excision of the aneurysm are required. This may be employed when the continuity of blood flow need not be maintained for viability or function or when an adequate collateral circulation has developed due to the gradual occlusion of the primary vessel. In large vessels where the blood flow must be maintained, reconstruction of the artery may be accomplished by a simple end-to-end anastomosis following resection of the necrotic tissue and aneurysm, or through the interposition of a graft.[6,14,16,20,33]

SUMMARY

Mycotic aneurysms are relatively infrequent but their marked propensity for rupture demands early recognition and prompt therapy if the patient is to survive. The nonspecific clinical findings make the diagnosis difficult. Any mass associated with evidence of present or past infection should be suspect. Angiography will almost always delineate the aneurysms. Treatment consists of intense, appropriate antibiotic therapy, excision of the aneurysm and re-establishment of blood vessel continuity where essential.

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CHRONIC POST-THROMBOTIC OBSTRUCTION OF THE INFERIOR VENA CAVA INVESTIGATED BY CAVOGRAPHY*

A REPORT OF 11 CASES

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THE most commonly described physical signs of chronic obstruction of the inferior vena cava are bilateral swelling of the legs and the presence of superficial abdominal wall collateral veins in which the blood-flow is towards the head.[8,11,12,16] These collaterals, the superficial epigastric and superficial circumflex iliac veins, arise at the sapheno-femoral junction and are only present when the obstruction extends into the external iliac veins. Many cases of inferior vena caval obstruction involve the inferior vena cava alone, and no superficial collaterals are visible.

Bilateral edema of the legs, due to inferior vena caval obstruction may not be distinguishable on clinical grounds from bilateral iliac vein obstruction.

Should surgical treatment for inferior vena caval obstruction, either by thrombectomy or by-pass procedures be contemplated, it is essential not only to diagnose the condition but also to show the full extent of the lesion before its suitability for surgery, and the method which may be employed, can be assessed.

Inferior vena cavography is the most reliable method available for the diagnosis of inferior vena caval obstruction and to show its extent.[2,3,8]

In this paper we describe the methods of cavography we have used and the findings in 11 patients with chronic post-thrombotic inferior vena caval obstruction.

MATERIAL AND METHODS

Eleven patients, 3 female and 8 male, whose ages ranged from 24 to 51 years (average 37 years) were investigated by percutaneous femoral cavography; 5 by pertrochanteric cavography; and 3 by a combination of these two techniques together. In addition 2 of the patients had transcardiac catheterization cavography to show the upper part of the inferior vena cava.

1. PERCUTANEOUS PERFEMORAL CAVOGRAPHY

With the patient in the supine position, under either general or local anesthesia, both common femoral veins are punctured percutaneously, using a Sheldon cannula,[15] which is threaded up the veins for a few centimeters.

Forty milliliters of conray 420 are injected simultaneously on each side by hand. Ten 14 × 14 inch films of the pelvis and lower abdomen are exposed at a rate of 1 per second, the filming and injection being started at the same time. This series of films is then examined and if the upper end of the obstruction of the inferior vena cava has not been demonstrated the examination is repeated centering over the upper abdomen and thorax. These films are exposed slightly later than the first series—the exact timing being based on a study of the previous run.

2. PERTROCHANTERIC INTRA-OSSEOUS CAVOGRAPHY

With the patient in the prone position, under general anesthesia, heavy duty gauge bone marrow needles are introduced into both greater trochanters under television control.

Forty milliliters of conray 420 are injected through each needle simultaneously using gas operated pressure pumps set at 40 lb. per square inch. Films of the pelvis and lower abdomen are exposed as described

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TABLE I

SUMMARY OF CASES

Case No.	Age and Sex	Presenting Symptoms	Possible Precipitating Cause	Clinical Diagnosis	Superficial Abdominal Veins	Albuminuria, Blood Urea (mg./100 ml.)	Phlebographic Technique	Site of Obstruction Demonstrated by Phlebography
1	51 F	Swollen thighs and legs with ulceration for 20 years	Pregnancy followed by deep vein thrombosis	Varicose veins of legs with incompetent valves	None	Albumin—none Blood Urea—not measured	Prone bilateral pertrochanteric	Inferior vena cava obstruction extending above the renal veins
2	30 M	Swollen thighs and legs for 11 years	Appendiceal abscess treated conservatively	Bilateral iliac venous thrombosis; inferior vena cava possibly involved	None	Albumin—trace Blood Urea—34	Supine bilateral perfemoral	Inferior vena cava obstruction
3	25 M	Swollen left leg with ulcer of left ankle for 7 years	16 weeks bed rest for pneumonia; left deep leg vein thrombosis	Left common iliac vein occlusion	None	Albumin—none Blood Urea—not measured	Supine bilateral perfemoral	Inferior vena cava obstruction extending above the renal veins
4	24 M	Swollen legs, venous claudication, varicose veins for 6 years	Injury to legs	Thrombo-phlebitis of both legs	Anterior abdominal wall	Albumin—none Blood Urea—not measured	Supine bilateral pertrochanteric	Inferior vena cava obstruction extending above the renal veins with bilateral common and external iliac vein recannalisation
5	50 F	Swollen legs, varicose veins, and ulcers of both legs for 10 years	Deep vein thrombosis after hysterectomy	Bilateral iliac vein and possibly inferior vena cava thrombosis	Anterior abdominal wall	Albumin—none Blood Urea—not measured	Prone bilateral pertrochanteric	Inferior vena cava, bilateral common and external iliac vein obstruction extending above the renal veins
6	51 F	Swollen legs, varicose veins for 25 years	Pregnancy followed by bilateral deep vein thrombosis	Longstanding bilateral iliac vein occlusion	None	Albumin—none Blood Urea—23	Supine bilateral perfemoral	Low inferior vena cava recanalisation below renal veins; bilateral common and external iliac vein recanalisation
7	35 M	Swollen legs, varicose veins and ulceration for 7 years	Pyelitis treated by bed rest for 1 week	Inferior vena cava occlusion	Anterior abdominal wall	Albumin—trace Blood Urea—24	Prone bilateral pertrochanteric	Inferior vena cava obstruction extending above the renal veins with bilateral common and external iliac vein recanalisation
8	37 M	Swollen legs for 1 year; deep leg vein thrombosis three times in the last 2 years	None	Longstanding bilateral iliac vein and deep leg vein thrombosis	None	Albumin—none Blood Urea—28	Supine left pertrochanteric, right perfemoral	Low inferior vena cava obstruction below the renal veins with left common and external iliac vein obstruction
9	24 M	Swollen thighs and legs, varicose ulcer of left leg for 2 years	Injury to left groin followed by 1 week in bed and deep vein thrombosis	Inferior vena cava obstruction	Anterior abdominal wall	Albumin—none Blood Urea—not measured	Supine bilateral pertrochanteric; transcardiac cavography	Low inferior vena cava recanalisation below the renal veins; low inferior vena cava and bilateral common and external iliac vein obstruction
10	31 M	Swollen legs and venous claudication for 3 months	Influenza treated by 1 week bed rest	Inferior vena cava obstruction	None	Albumin—0.5 gm. a day Blood Urea—27	Supine left pertrochanteric, right perfemoral; transcardiac cavography	Inferior vena cava and bilateral common and external iliac vein obstruction; recanalisation extending above the renal veins
11	48 M	Swollen legs for 1 year	Behçet's disease for 3 years	Inferior vena cava occlusion	Anterior abdominal and lateral chest wall	Albumin—none Blood Urea—25	Prone bilateral pertrochanteric	Low inferior vena cava obstruction below renal veins; bilateral common and external iliac vein obstruction

for the percutaneous femoral technique, except that the first film is exposed halfway through the injection of contrast medium. If the upper end of the obstruction has not been demonstrated a further series of films is exposed with later timing, centering over the upper abdomen and thorax after a further bilateral injection of contrast medium.

In 3 patients in whom percutaneous femoral venepuncture failed on one side, a combined technique was used, percutaneous femoral injection on one side and pertrochanteric intra-osseous injection on the other.

3. TRANSCARDIAC CATHETERIZATION CAVOGRAPHY

This method was used in 2 patients to demonstrate the upper end of the vena caval obstruction.

An N.I.H. dacron 8F angiography catheter is introduced through a cut down on the right basilic vein and passed under television control through the right atrium into the upper inferior vena cava. The catheter is then passed downwards to the site of obstruction and 40 ml. of contrast medium injected at a pressure of 60 lb. per square inch. A series of 5 films of the upper part of

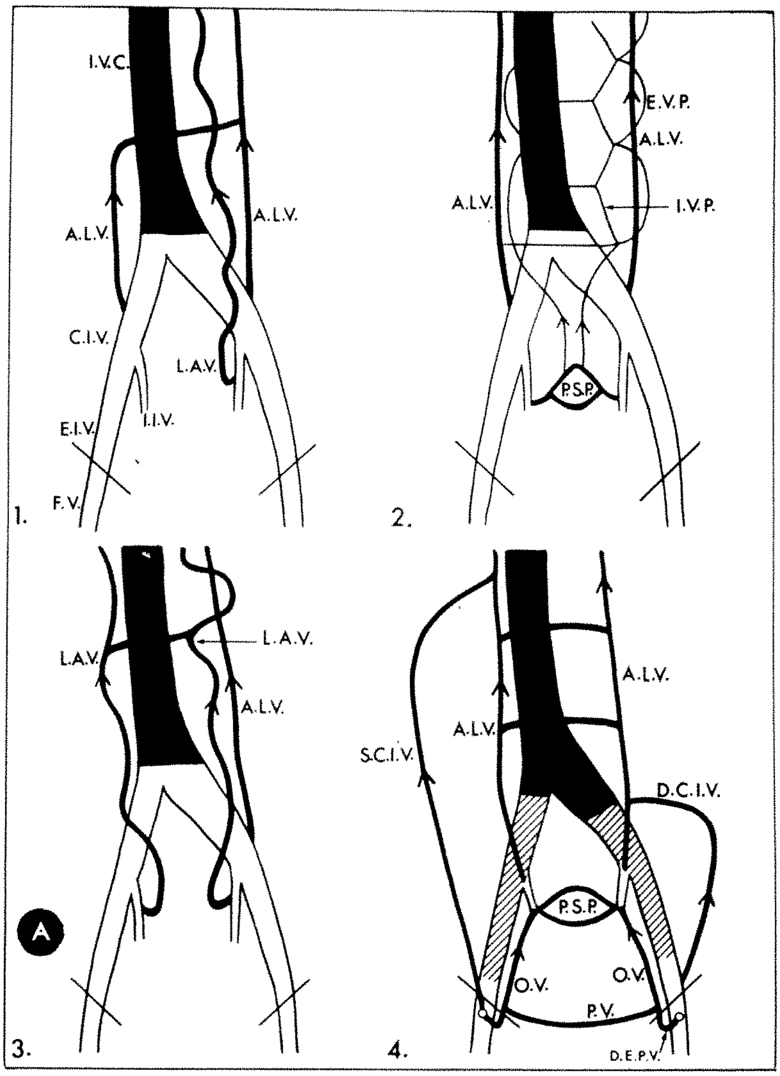

FIG. 1. (*A*) Diagrams of Cases 1 to 4 showing sites of obstruction and collaterals.

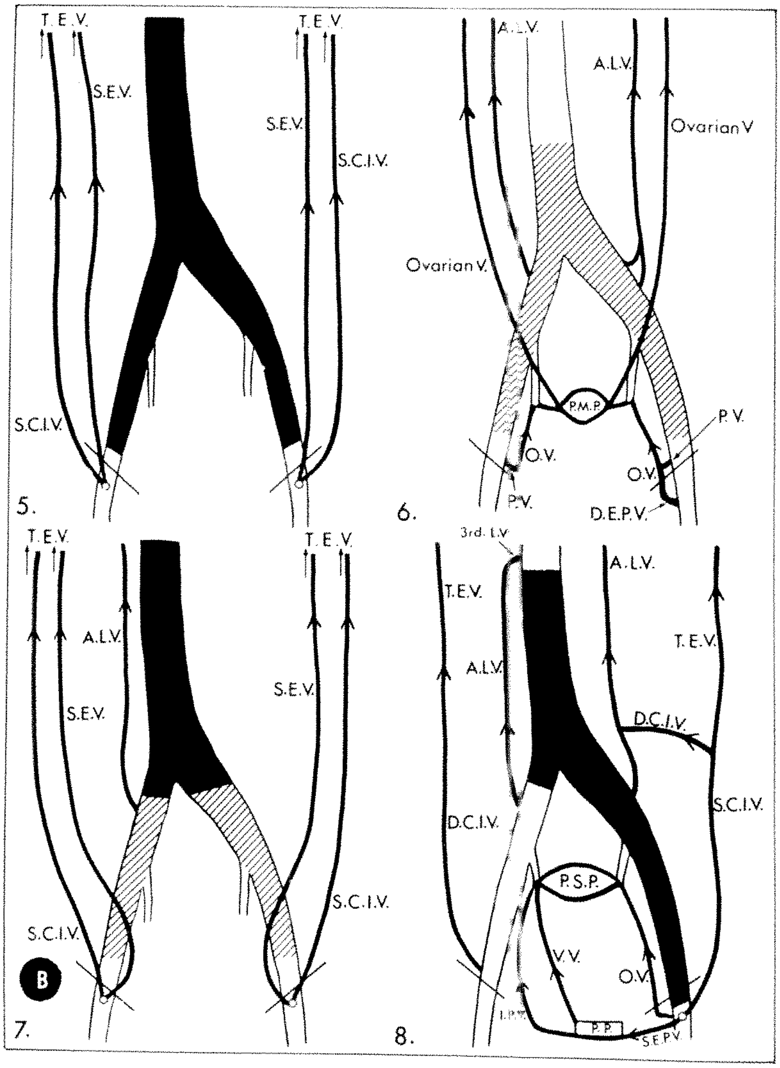

FIG. 1. (*B*) Diagrams of Cases 5 to 8 showing sites of obstruction and collaterals.

the inferior vena cava are exposed at the rate of 1 per second.

CLINICAL FEATURES

All the patients had edematous legs, the length of history ranging from 3 months to 25 years. Three patients had varicose ulcers and 2 complained of venous claudication. In 5 patients dilated veins were noted on the anterior abdominal wall with evidence of flow towards the head. Three patients had albuminuria; the blood urea was normal in the 6 patients in whom it was estimated.

The clinical features are summarized in Table 1.

RESULTS OF CAVOGRAPHY

SITES OF OBSTRUCTION

In 3 cases the inferior vena cava alone was totally obstructed. In the remaining 8 cases the iliac veins were also involved being either totally obstructed or narrowed by past thrombosis.

In 5 cases the proximal end of the obstructed inferior vena cava was demonstrated by percutaneous femoral cavography, pertrochanteric cavography or by transcardiac catheterization cavography. In only 1 patient (Case 10) did we show by cavography that the renal veins were involved in the thrombotic process. The sites

of obstruction and whether it was partial or complete are shown in Figure 1, *A*, *B* and *C*.

COLLATERALS BY-PASSING THE OBSTRUCTION

Anterior abdominal wall collaterals with reverse flow have generally only been observed in those patients in whom the thrombotic process extended into the external iliac veins (Cases 4, 5, 7, 8, 9 and 11). The main collaterals in this group are the superficial circumflex iliac veins and the superficial epigastric veins which either enter the inferior vena cava above the obstruction through the subcostal veins or enter the axillary veins via the thoraco-epigastric veins[1,2,3,5,8,16] (Fig. 2, *A* and *B*; Case 11).

In those patients (Cases 1, 2 and 3) in whom the obstruction was confined to the inferior vena cava the collateral pathways were situated on the posterior abdominal wall and consist mainly of the ascending lumbar veins, the lumbo-azygos veins and the vertebral plexus[2,3,6] (Fig. 3). In many instances, in which both the inferior vena cava and the iliac veins have been involved in the thrombotic process, both anterior and posterior abdominal wall collaterals have been observed—the posterior abdominal wall collaterals filling through the obturator veins (Cases 4, 6, 8, 9, 10 and 11; Fig. 1, *A*, *B* and *C*).

In Case 10 (Fig. 4, *A*, *B* and *C*) in whom the inferior vena cava and both common and external iliac veins were totally obstructed, the collateral flow was mainly through the recto-vesical plexus and inferior mesenteric vein to enter the portal system, and no anterior abdominal wall collaterals were demonstrated.

DISCUSSION

Percutaneous perfemoral cavography[1,5,9,14] is a simpler method than pertrochanteric intra-osseous cavography[13,14] and has the advantage that it can be performed under local anesthesia. If the femoral veins are involved in thrombosis, however, venepuncture may not be possible and under

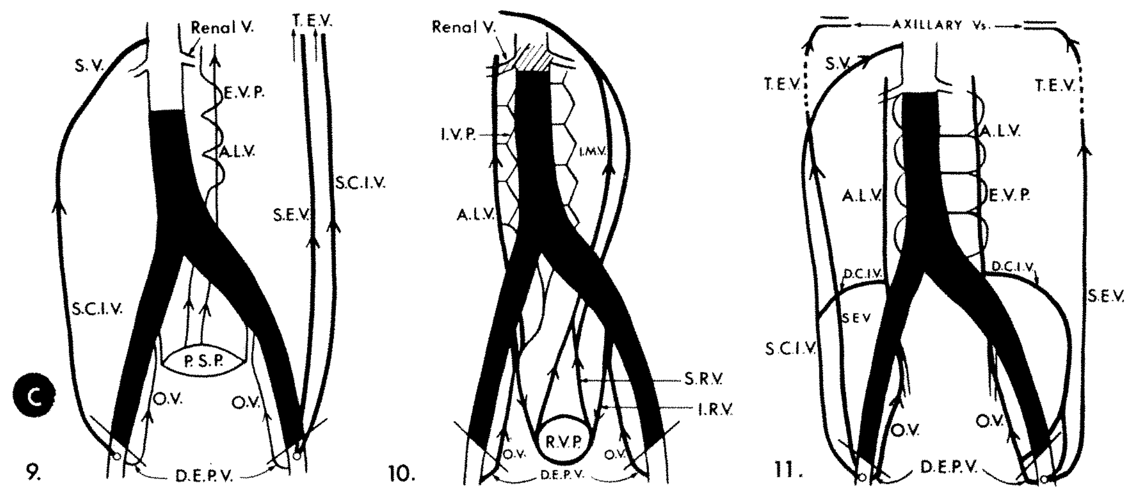

FIG. 1. (*C*) Diagrams of Cases 9 to 11 showing sites of obstruction and collaterals.

Partial Obstruction

Total Obstruction

Key to abbreviations: A.L.V.—Ascending Lumbar Vein; C.I.V.—Common Iliac Vein; D.C.I.V.—Deep Circumflex Iliac Vein; D.E.P.V.—Deep External Pudendal Vein; E.I.V.—External Iliac Vein; E.V.P.—External Vertebral Plexus; F.V.—Femoral Vein; I.I.V.—Internal Iliac Vein; I.M.V.—Inferior Mesenteric Vein; I.P.V.—Internal Pudendal Vein; I.R.V.—Inferior Rectal Vein; I.V.C.—Inferior Vena Cava; I.V.P.—Internal Vertebral Plexus; L.A.V.—Lumbo-Azygos Vein; L.V.—Lumbar Vein; O.V.—Obturator Vein; P.M.P.—Parametrial Plexus; P.P.—Pudendal Plexus; P.S.P.—Presacral Plexus; P.V.—Pubic Vein; R.V.P.—Recto-Vesical Plexus; S.C.I.V.—Superficial Circumflex Iliac Vein; S.E.P.V.—Superficial External Pudendal Vein; S.E.V.—Superficial Epigastric Vein; S.R.V.—Superior Rectal Vein; S.V.—Subcostal Vein; T.E.V.—Thoraco-epigastric Vein; V.V.—Vesical Vein; 3rd L.V.—Third Lumbar Vein.

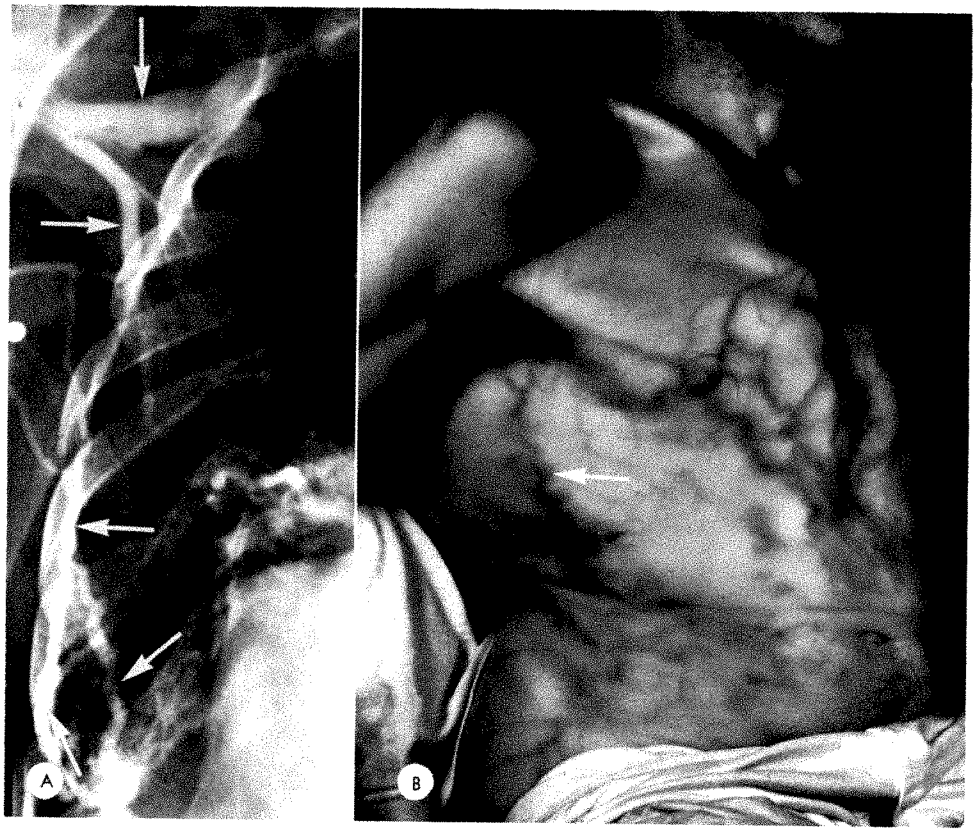

FIG. 2. Case 11. (*A*) Pertrochanteric intra-osseous cavogram showing the right lateral thoracic vein (→) entering the right axillary vein (↓). Right thoraco-epigastric vein (←); right superficial epigastric vein (↙); right superficial circumflex iliac vein (↖). (*B*) Infrared photograph showing the superficial veins of the right anterior abdominal wall and the right lateral chest wall. Right thoraco-epigastric vein (←).

these circumstances pertrochanteric cavography has to be used. If in either method bilateral simultaneous injections of a large volume of contrast medium are made, the proximal end of an obstruction of the inferior vena cava can often be demonstrated by collateral filling. In Case 11, collateral veins arising from the sapheno-femoral junction were shown to enter the axillary vein by the intra-osseous technique (Fig. 2*A*). Transcardiac catheterization cavography[4,10,14] is regarded as a supplementary method to show the upper end of an occlusion if this has not been demonstrated by pelvic cavography.

No complications of the 3 methods of cavography were encountered in this series of patients.

An interesting clinical feature of this series of patients is that 9 out of 11 had a period of bed rest (sometimes with a deep leg vein thrombosis) immediately preceding the onset of symptoms;[8,11] other than this no precipitating causes could be found. Another interesting clinical feature is that in only 4 of the 11 patients was a definitive diagnosis of inferior vena caval obstruction made on clinical grounds, although in a further 2 cases it was suspected. In the remaining 5 patients the clinical diagnosis was either of iliac vein obstruction or varicose veins of the legs. As the clinical diagnosis depends on the recognition of anterior abdominal wall collaterals running towards the axillae, in the absence of these the diagnosis can not be made with confidence. For this reason inferior vena cavography is an essential diagnostic procedure. In order to assess the suitability of a patient for surgical treatment whether by by-

pass procedures or thrombectomy, the exact site and full extent of the inferior vena caval obstruction must be known. Although albuminuria is a constant feature of acute thrombosis of the inferior vena cava involving the renal veins,[4,8,11] in these chronic cases albuminuria was either absent or only present in small amounts, and for this reason albuminuria cannot be relied upon as evidence of involvement of the renal veins in the thrombotic process. In Case 2, in whom the proximal end of the obstruction was not demonstrated by pelvic cavography it was assumed that the obstruction did not extend to involve the renal veins, as he only had a trace of albuminuria. At operation, however, the whole of the inferior vena cava, as far as the right atrium, was found to be obstructed and no surgical procedure could be undertaken. For this reason we now believe that if the upper end of the obstruction has not been demonstrated by pelvic cavography, transcardiac catheterization cavography is essential in the assessment of suitability for surgical treatment.

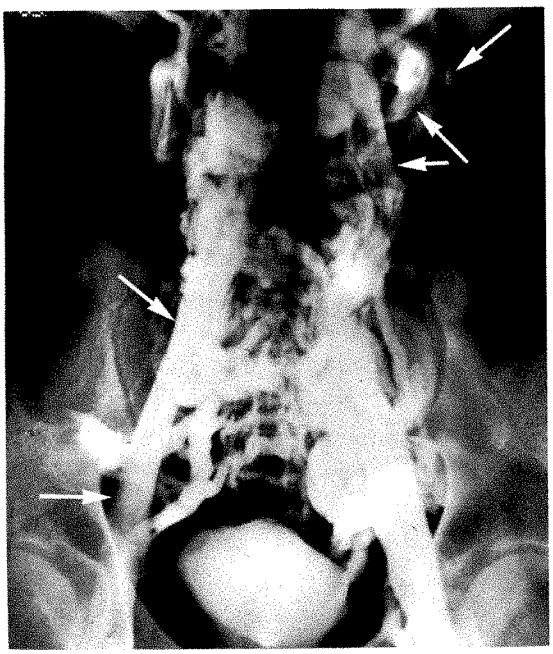

FIG. 3. Case 3. Bilateral perfemoral cavogram showing posterior abdominal wall collaterals. Right external iliac vein (→); right common iliac vein (↘); straight left ascending lumbar vein (←); tortuous lumbo-azygos vein (↖) displacing the left ureter (↙).

SUMMARY

Eleven patients with chronic post-thrombotic obstruction of the inferior vena cava have been investigated by cavography.

The clinical features and the roentgenologic techniques used are described.

The importance of inferior vena cavography in both the diagnosis of inferior vena caval obstruction and to show its extent is emphasized.

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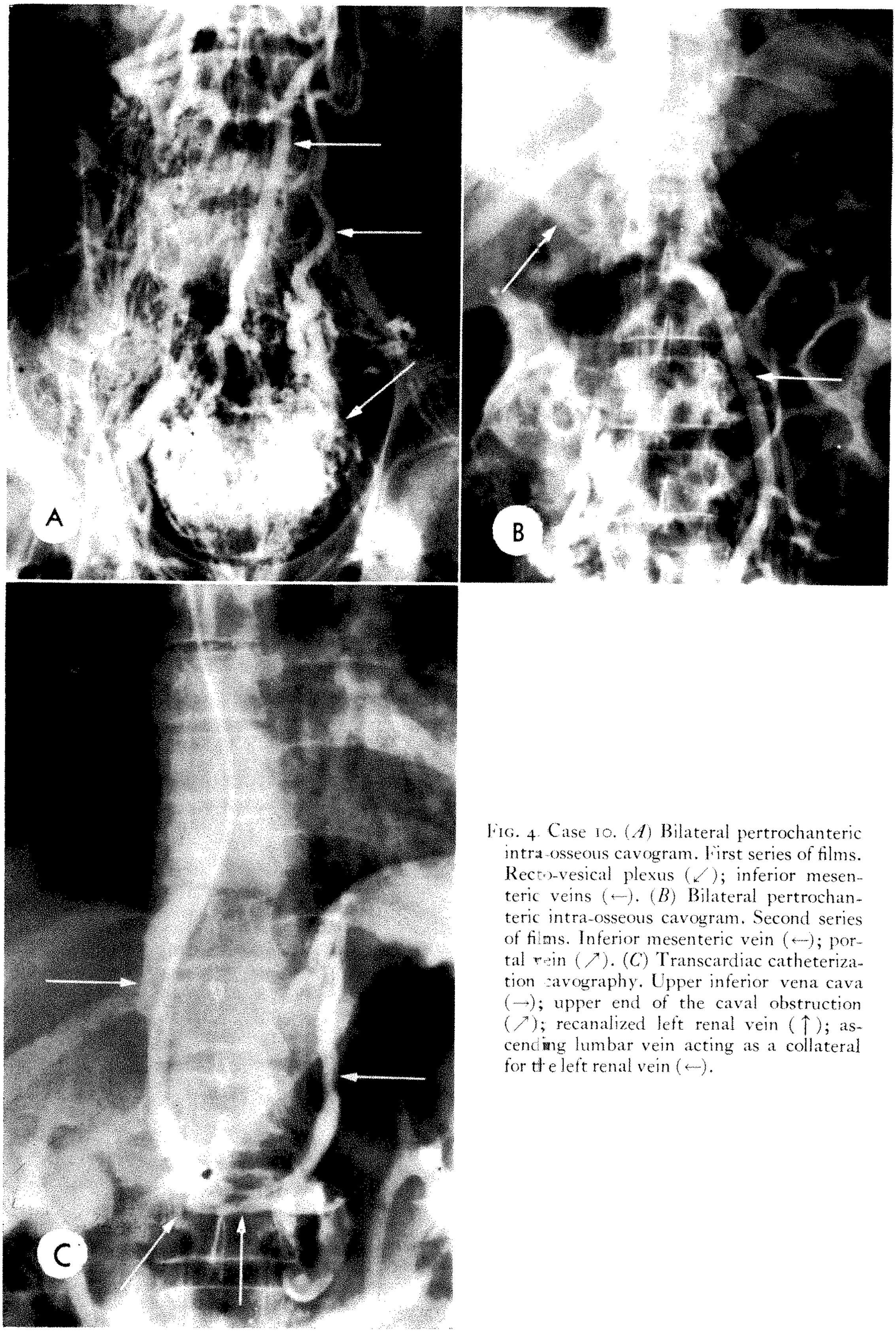

FIG. 4. Case 10. (*A*) Bilateral pertrochanteric intra-osseous cavogram. First series of films. Recto-vesical plexus (↙); inferior mesenteric veins (←). (*B*) Bilateral pertrochanteric intra-osseous cavogram. Second series of films. Inferior mesenteric vein (←); portal vein (↗). (*C*) Transcardiac catheterization cavography. Upper inferior vena cava (→); upper end of the caval obstruction (↗); recanalized left renal vein (↑); ascending lumbar vein acting as a collateral for the left renal vein (←).

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A PLAIN FILM SIGN OF TOTAL ANOMALOUS PULMONARY VENOUS CONNECTION BELOW THE DIAPHRAGM

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AMONG infants presenting with cyanosis and/or respiratory distress in the newborn period, total anomalous pulmonary venous connection (T.A.P.V.C) below the diaphragm is an important differential diagnostic consideration. This is especially true in the *immediate* newborn period when the distinction between complex congenital heart disease and primary respiratory disorders is difficult. Moreover, the problem of diagnosis is compounded further because the electrocardiogram and clinical signs of congestive heart failure are not clear cut in the first few days of life.

Differentiation, however, is important because T.A.P.V.C. below the diaphragm is a diagnostic and surgical emergency, whereas pulmonary diseases (hyaline membrane disease, pneumonia etc.) obviously require intensive medical treatment. Thus, it seems that any additional roentgen sign which would distinguish or at least point towards T.A.P.V.C. below the diaphragm rather than a primary pulmonary disorder would be of considerable aid.

In a recent case of T.A.P.V.C. below the diaphragm, an anterior indentation in the barium filled esophagus just above the diaphragm was observed. The significance of this indentation was puzzling because it was slightly below the expected esophageal impression of left atrial enlargement. Moreover, the one roentgen hallmark of all forms of T.A.P.V.C. is absence of left atrial enlargement.

In retrospect, the angiocardiographic and plain film findings of the esophageal indentation correlated precisely with the site of confluence formed by the veins draining both lungs. This confluence is often termed the "common pulmonary vein." Because of this finding, we reanalyzed the plain films and angiocardiograms in 5 additional cases of T.A.P.V.C. below the diaphragm. Much to our chagrin, barium swallow studies had been performed in only 2 of the additional 5 cases; yet in these 2 cases as in the aforementioned case, the same indentation in the esophagus was present. Therefore, the purpose of this paper is to briefly present the plain film findings in 3 cases of T.A.P.V.C. below the diaphragm as (1) a means of emphasizing a sign which may have considerable value in diagnosis, and (2) emphasizing the importance of esophagrams in all newborns with respiratory symptoms.

Definition of Terms. T.A.P.V.C. without additional complicating defects may be classified into two major types: (1) T.A.P.V.C. above the diaphragm (Fig. 1, *a* and *b*), and (2) T.A.P.V.C. below the diaphragm (Fig. 2). The latter type is the primary concern in this communication.

Infants with the infra-diaphragmatic type are often symptomatic in the immediate newborn period, whereas those with the supra-diaphragmatic type usually manifest symptoms somewhat later (2–3 months).

MATERIAL AND RESULTS

The basic material consists of 3 cases of T.A.P.V.C. below the diaphragm. The final site of drainage was the portal vein.

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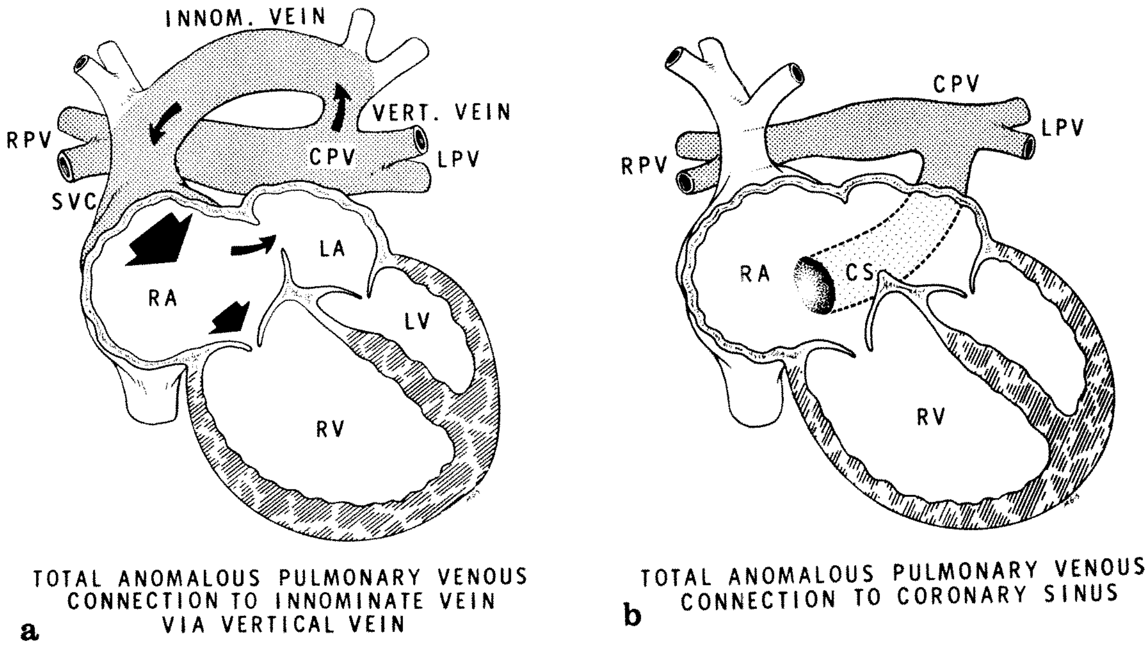

Fig. 1. Schematic representation of the supra-cardiac type of total anomalous pulmonary venous connection (T.A.P.V.C.). (*a*) Most common type at the supra-cardiac level. Right and left pulmonary veins (RPV, LPV) form the common pulmonary (CPV) from which the so-called "vertical vein" connects with the innominate vein. As a result, all pulmonary venous blood empties into the right atrium (RA). Arrows indicate direction of flow. Blood can only reach the left heart by an atrial septal defect. (*b*) Another common type at the cardiac level. The anomalous vein, after arising from the common pulmonary vein (CPV) connects with the coronary sinus (CS). SVC = superior vena cava, LA = left atrium, RV = right ventricle, and LV = left ventricle. (From Elliott, L. P., and Schiebler, G. L., with permission of Charles C Thomas.[1])

The ages were 3 days, 1 week and 3 weeks; all cases were males. Each case was proven by angiocardiography and necropsy. An additional case of T.A.P.V.C. above the diaphragm will be discussed in the comment section to emphasize our findings.

Plain Film Findings. The lungs exhibited a fine generalized reticulation and the heart was normal in size (Fig. 3, *a–d;* and 4, *a–d*). These findings are well known for this condition and have been described by

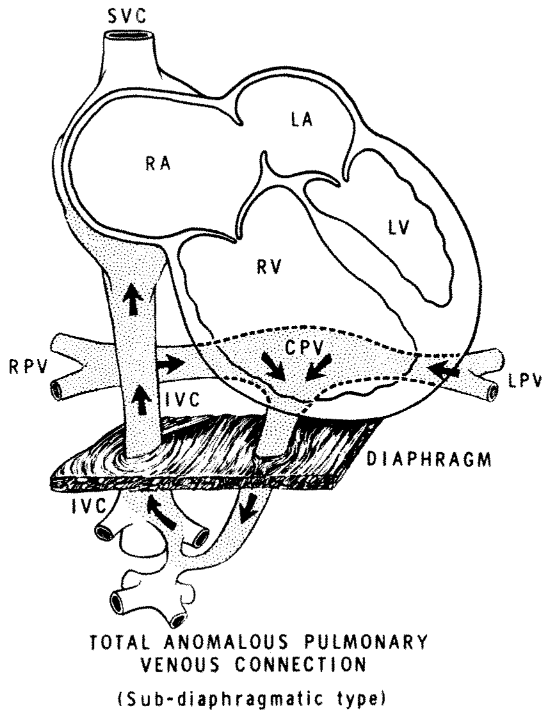

Fig. 2. Schematic representation of the infra or sub-diaphragmatic type of T.A.P.V.C. Abbreviations as in Figure 1. Right and left pulmonary veins (RPV, LPV) form the common pulmonary vein (CPV) a short distance above the diaphragm. An anomalous vein passes through the diaphragm to connect with the portal system. Arrows indicate direction of pulmonary blood flow. IVC = inferior vena cava.

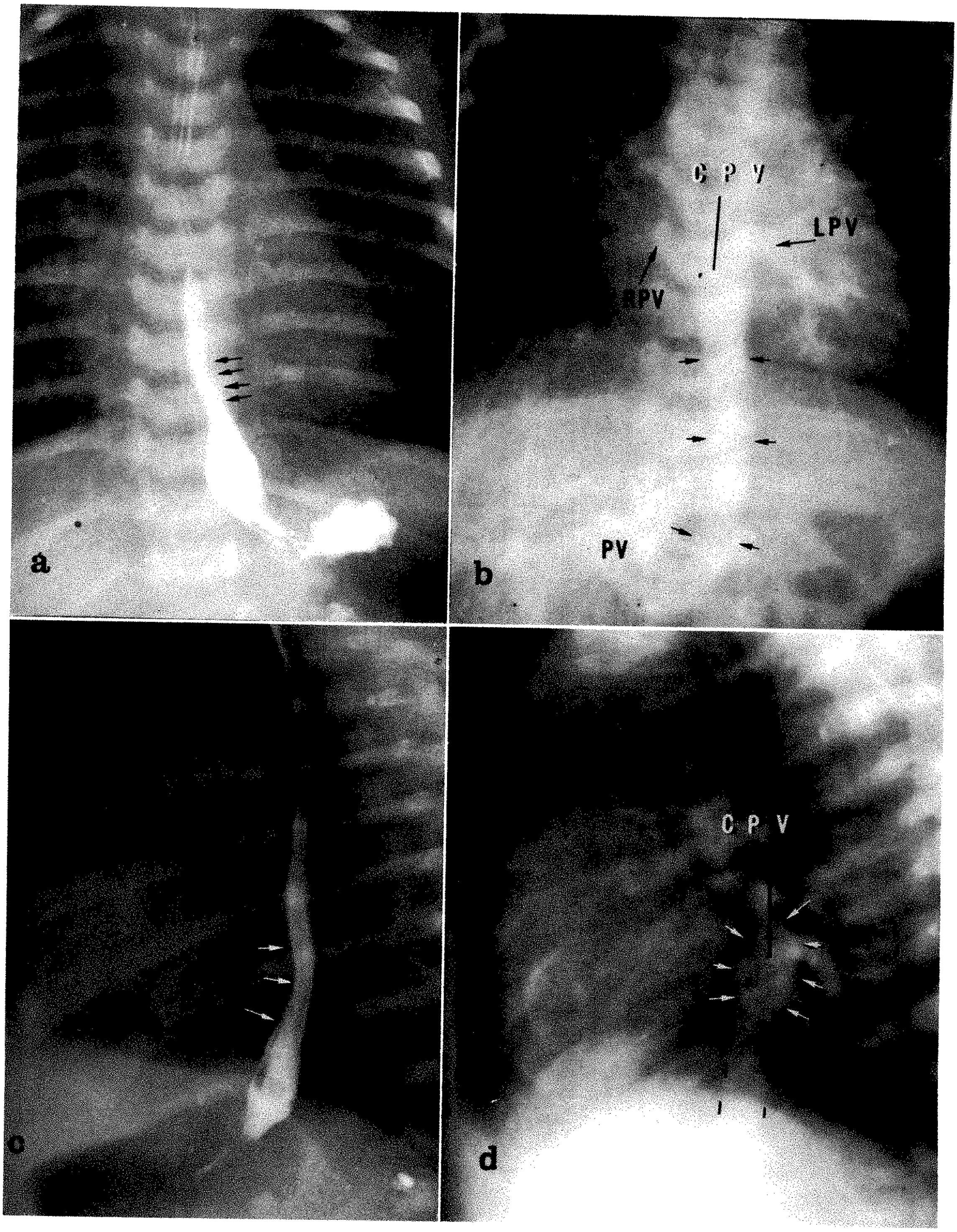

FIG. 3. T.A.P.V.C. below the diaphragm in a 3 day old male. Abbreviations as in Figure 1. The posteroanterior (*a*) and lateral (*c*) chest roentgenograms show a low anterior indentation (arrows) in the barium filled esophagus owing to compression from the common pulmonary vein (CPV). The indentation in *a* is only suggestive. Venous phase of the anteroposterior (*b*) and lateral (*d*) angiocardiograms. The CPV is faintly opacified. It is situated immediately anterior to the esophagus and produces the aforementioned indentations. An anomalous vein (arrows in *b*) arises from the CPV, descends through the diaphragm and enters the portal system (PV).

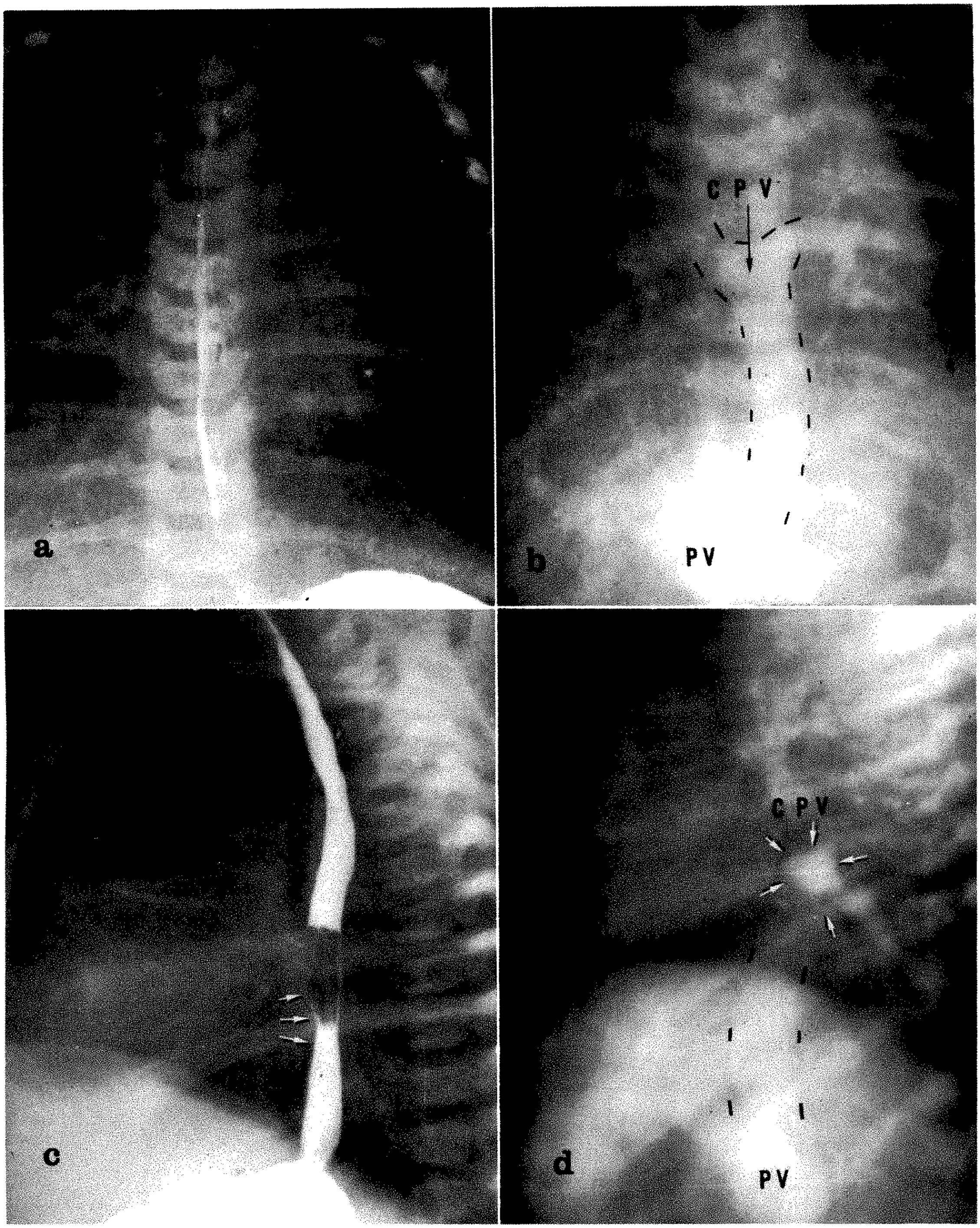

Fig. 4. One week old male infant with T.A.P.V.C. below the diaphragm. Abbreviations and findings as in Figure 3. (*a–d*) The correlation between the CPV and the esophageal indentation is again demonstrated. Small hatched lines in *b* and *d* show the long anomalous vein descending through the diaphragm to enter the portal system (PV). The indentation in *c* is smaller than in Figure 3 because the CPV itself is relatively smaller.

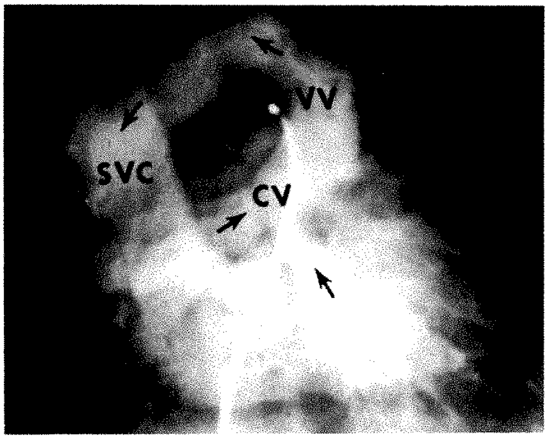

Fig. 5. Venous phase of the pulmonary arteriogram in a case of T.A.P.V.C. above the diaphragm. The right and left pulmonary veins converge to form the common pulmonary vein (CV). From the common pulmonary vein venous blood is drained to the innominate vein via the so-called vertical vein (VV). Flow continues to the superior vena cava (SVC), right atrium, etc. Arrows denote direction of blood flow.

other investigators.[2,3] Additionally, however, each case demonstrated a small localized indentation in the anterior aspect of the barium filled esophagus just above the diaphragm (Fig. 3, *a* and *c;* and 4, *a* and *c*). This was seen in 3 of the 4 cardiac views except the left anterior oblique view. However, the lateral view was the only projection in which this sign was conclusive (Fig. 3*c;* and 4*c*).

Angiocardiographic Findings. During the pulmonary venous phase of angiocardiography, the right and left pulmonary veins converged to form a *midline* confluence (common pulmonary vein) directly behind the lower aspect of the heart, immediately anterior to the esophagus (Fig. 3, *b* and *d;* and 4, *b* and *d*). In each case, the position of the common pulmonary vein coincided precisely with the plain film esophageal indentation (Fig. 3, *c* and *d;* and 4, *c* and *d*). An anomalous vein arose from the venous confluence to course inferiorly through the diaphragm and connect with the portal vein.

The venous confluence in the additional 3 cases in whom the esophagus was not outlined was located in the same position as the cases reported herein. The fact that barium study was withheld in these cases was doubly unfortunate, because the decision to perform cardiac catheterization was delayed in 2 of these cases.

COMMENT

Total anomalous pulmonary venous connection (T.A.P.V.C.) below the diaphragm may mimic the more common respiratory diseases of the newborn infant. In this condition, the common pulmonary vein is characteristically located in the midline behind the heart and anterior to the esophagus. In our limited experience, this results in a small, localized indentation in the barium filled esophagus. Casual inspection may lead the observer to conclude that this represents compression by the left atrium. However, closer examination shows the summit of the indentation caused by the dilated common pulmonary vein to be below the maximum point of esophageal indentation seen usually in left atrial enlargement.

The general tendency in some hospitals is to lavish barium examination on the sick infant with apparent congenital heart disease, but forego this procedure in infants with apparent pulmonary disease. Fear of pulmonary aspiration seems to be one of the prime reasons to forego esophageal visualization in these cases. However, there exists no group of patients which warrants contrast visualization of the esophagus more than the infant with respiratory distress. Digitalis and antibiotics have yet to cure a diaphragmatic hernia, vascular ring, etc.

In the preparation of this paper, it was our opinion that this sign occurred only in patients with the infra-diaphragmatic type of T.A.P.V.C. In the supra-diaphragmatic type, the venous confluence occurs more cephalad and to the left of midline (Fig. 5). Moreover, the patho-physiology between the two major types are so different, that plain film findings usually suffice in distinguishing them.

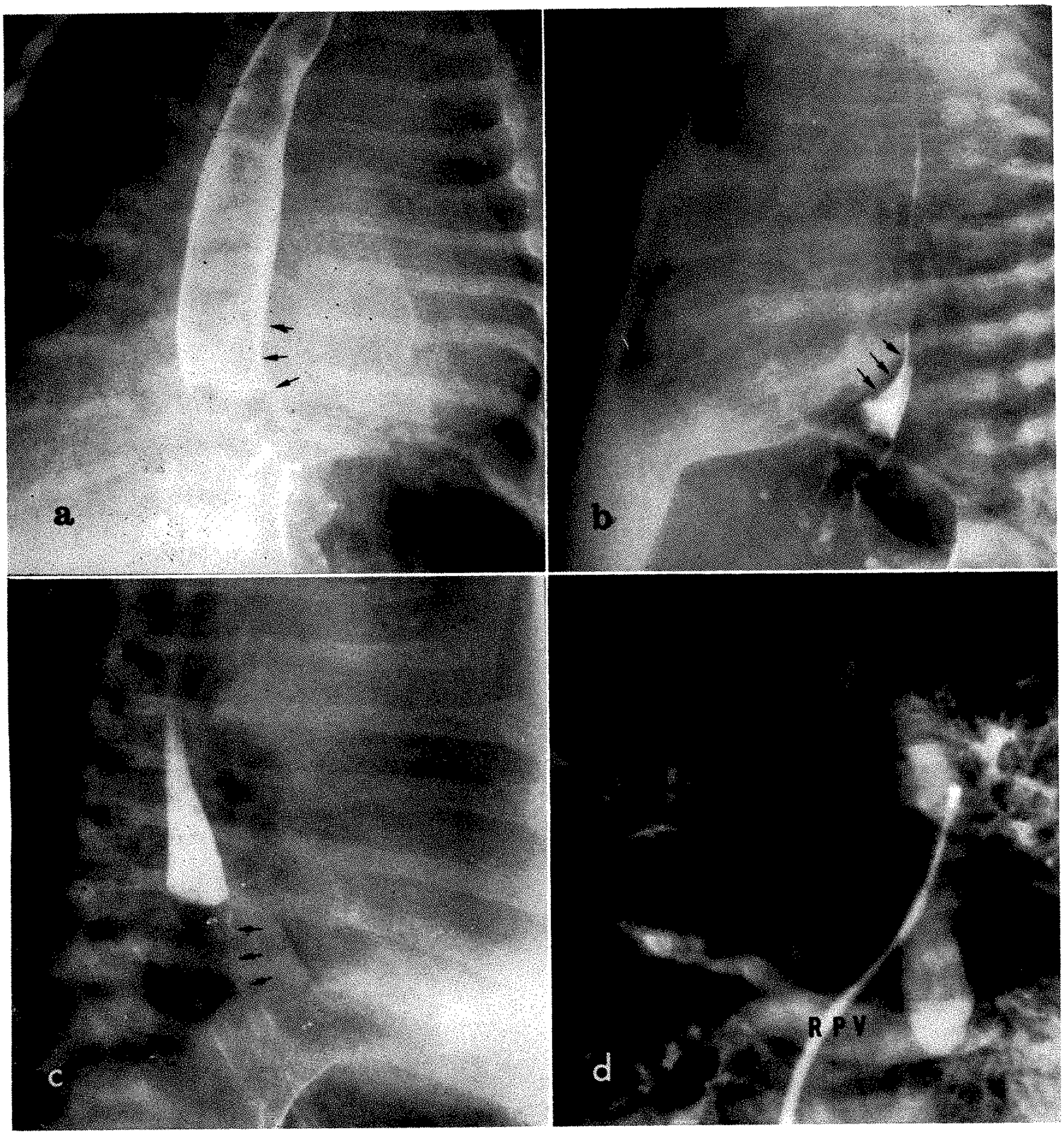

Fig. 6. Six week old male with T.A.P.V.C. above the diaphragm. There is an indentation (arrows) in the low anterior aspect of the esophagus similar to the aforementioned cases. This is evident in the (*a*) postero-anterior, (*b*) lateral and (*c*) right anterior oblique views. (*d*) Venous phase of a selective pulmonary arteriogram. The esophageal indentation is produced by the large right pulmonary vein (RPV) as it courses across the midline to form a confluence with the vein draining the left lower lobe.

Recently, a case which proved to be an unusual type of T.A.P.V.C. above the diaphragm showed an identical indentation in the esophagus as in the infradiaphragmatic type (Fig. 6, *a–c*). However, the clinical and other plain film findings did not support the diagnosis of infradiaphragmatic T.A.P.V.C. As a result, cardiac catheterization was performed with several working diagnoses. Because of our current interest, some unusual form of venous anomaly was considered.

Pulmonary arteriography (Fig. 6*d;* and 7, *a* and *b*) demonstrated the veins drain-

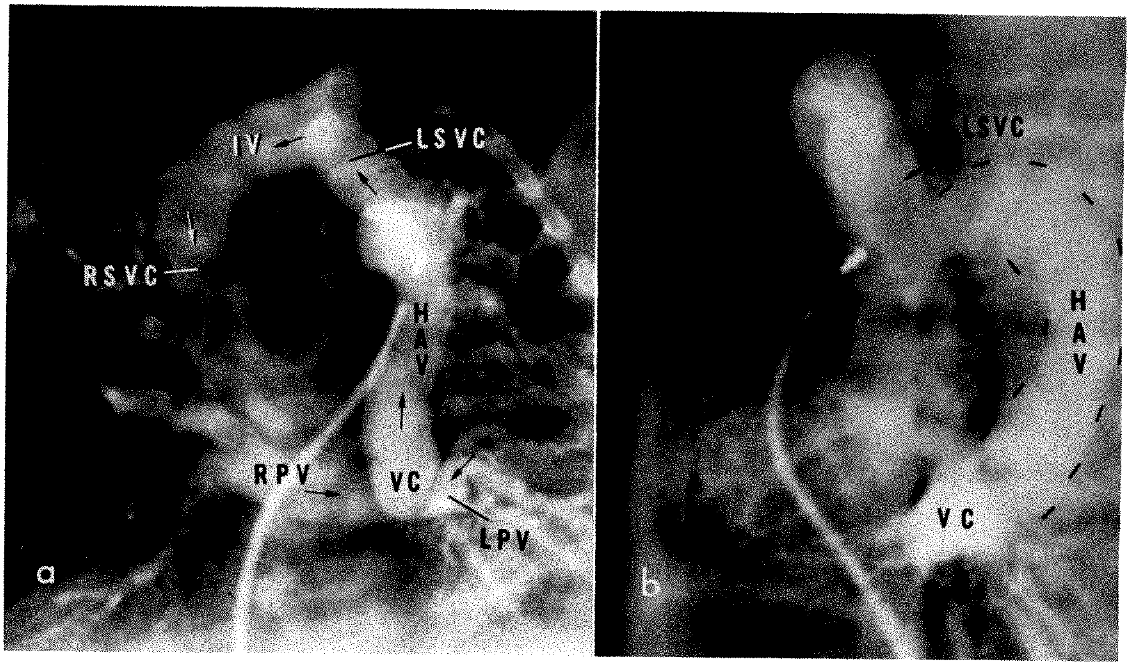

Fig. 7. Same case as in Figure 6. Slightly later period in the venous phase of the pulmonary arteriogram. (*a*) Anteroposterior view. (*b*) Lateral view. The RPV joins the left lower lobe pulmonary vein (LPV) to form the venous confluence (VC). From the VC, blood flows cephalad via a large posterior hemiazygous vein (HAV). In the superior posterior portion of the left thorax, the hemiazygous vein courses anteriorly to join a left superior vena cava (LSVC). At the site of the hemiazygous vein and LSVC, the left upper lobe vein enters also. From this point, all the pulmonary blood flows into the innominate vein (IV) via the LSVC. Flow continues to the right atrium via the right superior vena cava (RSVC). Arrows denote the direction of blood flow. The vein entering the IV in this case is a true LSVC, rather than a vertical vein, because the hemiazygous vein is connected to it. The latter is a fundamental definition of a LSVC.

ing the entire right lung and lower lobe of the left lung to form a venous confluence behind the heart at the same level seen in the infra-diaphragmatic type of T.A.P.V.C. In contrast to the latter type, however, the site of junction of these veins was to the *left* of *midline* (Fig. 6*d*). Instead, the large venous channel of the right lung indented the anterior esophagus as it coursed across the midline (Fig. 6*d*).

This case was introduced simply to show that esophageal indentation owing to anomalous venous connections occurs in both major types of T.A.P.V.C. The remaining angiocardiographic findings will be explained in the legend of Figure 7, *a* and *b*.

One of the important facts to be gained from the latter case is that atypical indentations in the esophagus of any patient with congenital heart disease may represent some form of anomalous venous connection.

Lastly, it should be pointed out that this esophageal sign serves as one possible means of distinguishing T.A.P.V.C. below the diaphragm from other less common causes of severe pulmonary venous obstruction—conditions such as atresia of the common pulmonary vein, stenosis of the individual pulmonary veins, etc.[4]

SUMMARY

In 3 cases of T.A.P.V.C. below the diaphragm, the common pulmonary vein produced an anterior indentation in the lower portion of the barium filled esophagus. This occurred a short distance above the diaphragm, yet slightly below the expected site of left atrial indentation. With

further experience, this may prove to be a uniformally diagnostic sign, especially if carefully controlled barium swallow study is performed in all infants with respiratory distress.

A rare type of T.A.P.V.C. above the diaphragm is reported to show that similar esophageal indentations are not specific for T.A.P.V.C. below the diaphragm.

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ANGIOGRAPHIC MANIFESTATIONS OF HYDATID DISEASE OF THE LIVER*

A REPORT OF TWO CASES

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HYDATID disease (echinococcosis) is a disease of world wide distribution which frequently affects the liver. There are two types. The more common type is the unilocular hydatid disease which is caused by the larva of *Echinococcus granulosus*. The rarer alveolar type due to *Echinococcus multilocularis* simulates a malignant neoplasm.

This report is concerned with unilocular hydatid disease, in the evolution of which the sheep is the definite host, the dog the intermediate host and man the accidental host. Approximately 70 per cent of hydatid cysts are located in the liver and the right lobe is affected in 85 per cent of these cases.[7] Distal organ involvement is uncommon when the liver is the site of hydatid cysts.[5] The plain roentgenographic features of hydatid disease have been well documented and were recently reviewed by Bonakdarpour.[2]

In the liver the cysts may be single or multiple and vary greatly in size. Hepatic arteriography is an accurate preoperative method of confirming the diagnosis and locating the cysts. The angiographic appearances in 2 cases are recorded.

The technique used was similar to that described by Ödman.[13] The celiac axis and superior mesenteric artery were catheterized separately and a series of anteroposterior and lateral roentgenograms were taken on a biplane film changer.

REPORT OF CASES

CASE I. A 25 year old student presented with abdominal swelling of 6 months' duration. On clinical examination there was enlargement of the liver extending to the iliac crest. Clinically there was no other abnormality. A clinical diagnosis of hydatid disease was confirmed by a positive Casoni skin test. The complement fixation test for hydatid disease was positive at a dilution of 1 in 32.

Arteriographic Appearances. (Fig. 1, *A*, *B* and *C*). The arterial phase showed displacement of the celiac axis to the left and downward displacement of the common hepatic artery. The intrahepatic arteries were markedly stretched and elongated. The venous hepatogram phase showed a patent portal vein and 4 avascular areas in the liver, 2 in the right lobe and 2 in the left lobe.

Four cysts were removed from the liver at operation.

CASE II. A 27 year old woman presented with abdominal swelling of 11 months' duration. Clinically there was no abnormality apart from marked enlargement of the liver. The Casoni skin test and the complement fixation test for hydatid disease were positive.

Arteriographic Appearances (Fig. 2, *A*, *B* and *C*). The arterial phase showed stretching and elongation of the intrahepatic arteries around the cysts. The venous hepatogram phase showed a patent portal vein and 5 avascular areas in the hepatic parenchyma. The outline of each cyst was clearly defined by contrast medium passing between the hydatid membrane and the pericystic layer in the venous hepatogram phase—a phenomenon which has been previously described at percutaneous transplenic portal venography in hydatid disease[15] but not at arterioportography.

Five cysts were removed from the liver at operation.

DISCUSSION

A survey of the literature in the English language reveals no previous reports of the arteriographic features of hydatid disease of the liver. Morino[11] reported the angiographic findings in 2 cases in the Italian literature.

At hepatic arteriography avascular areas in the liver may be due to:

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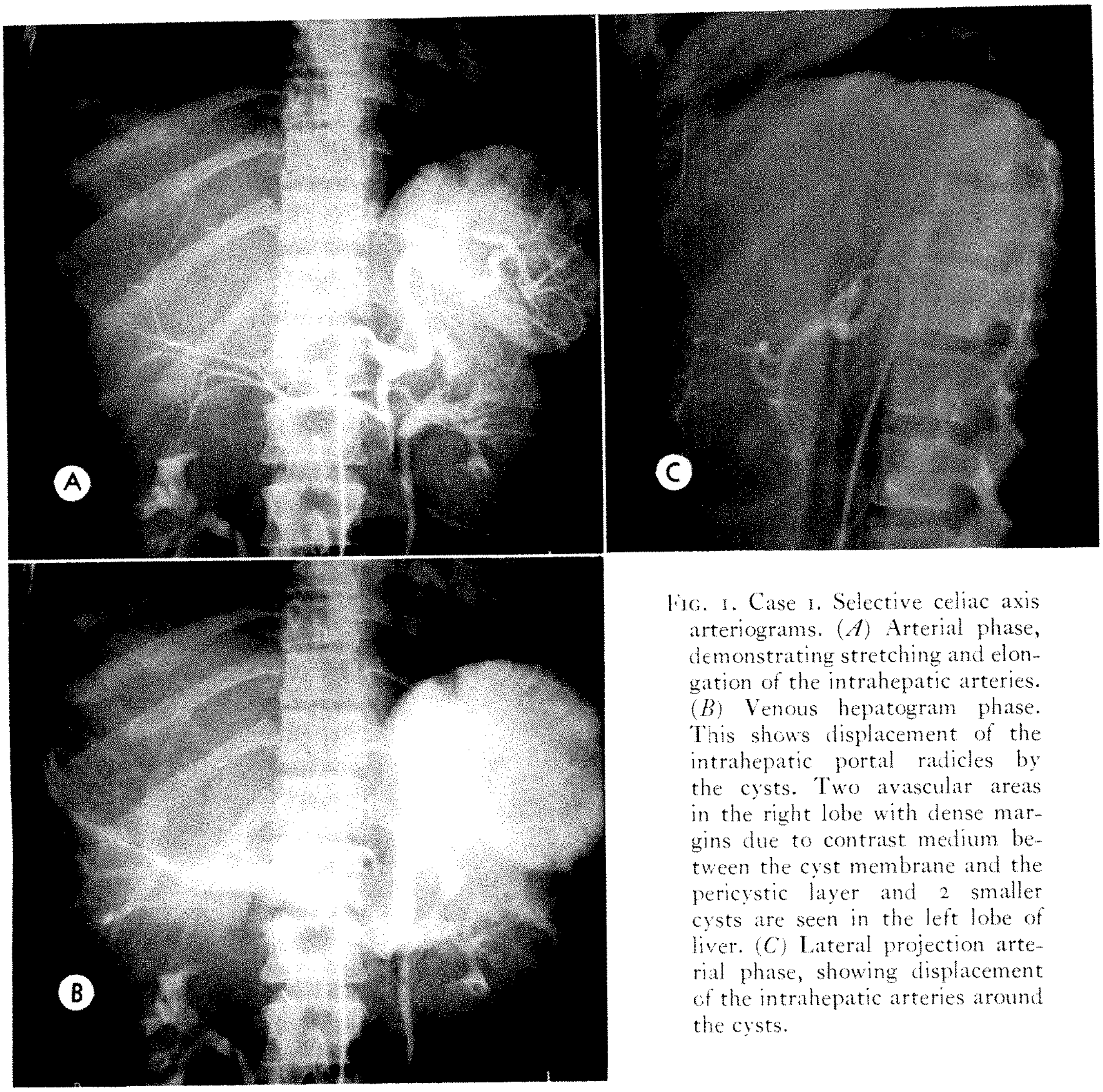

Fig. 1. Case 1. Selective celiac axis arteriograms. (*A*) Arterial phase, demonstrating stretching and elongation of the intrahepatic arteries. (*B*) Venous hepatogram phase. This shows displacement of the intrahepatic portal radicles by the cysts. Two avascular areas in the right lobe with dense margins due to contrast medium between the cyst membrane and the pericystic layer and 2 smaller cysts are seen in the left lobe of liver. (*C*) Lateral projection arterial phase, showing displacement of the intrahepatic arteries around the cysts.

(1) Anomalous origin of the hepatic arteries from the aorta, left gastric or superior mesenteric artery.[10] Hence, in investigating space occupying lesions of the liver it is always necessary to catheterize both the celiac axis and superior mesenteric artery, either successively or simultaneously.

(2) Congenital polycystic disease of the liver. This condition is associated with polycystic disease of the kidneys in approximately 50 per cent of cases.[6,9] The arterial phase may be similar to that seen in multiple hydatid cysts, but the characteristic appearance of contrast medium between the hydatid membrane and the pericystic layer is not seen.[14]

(3) Hematoma of the liver may present as an avascular area which may be accurately delineated by hepatic arteriography.[1] The source of bleeding, such as an aneurysm or a severed artery, may be demonstrated.

(4) A post-traumatic liver cyst, occurring several months after an abdominal injury, may present as an avascular area in the liver.[8]

(5) Solitary cysts including lymph cysts, dermoids, endothelial and solitary

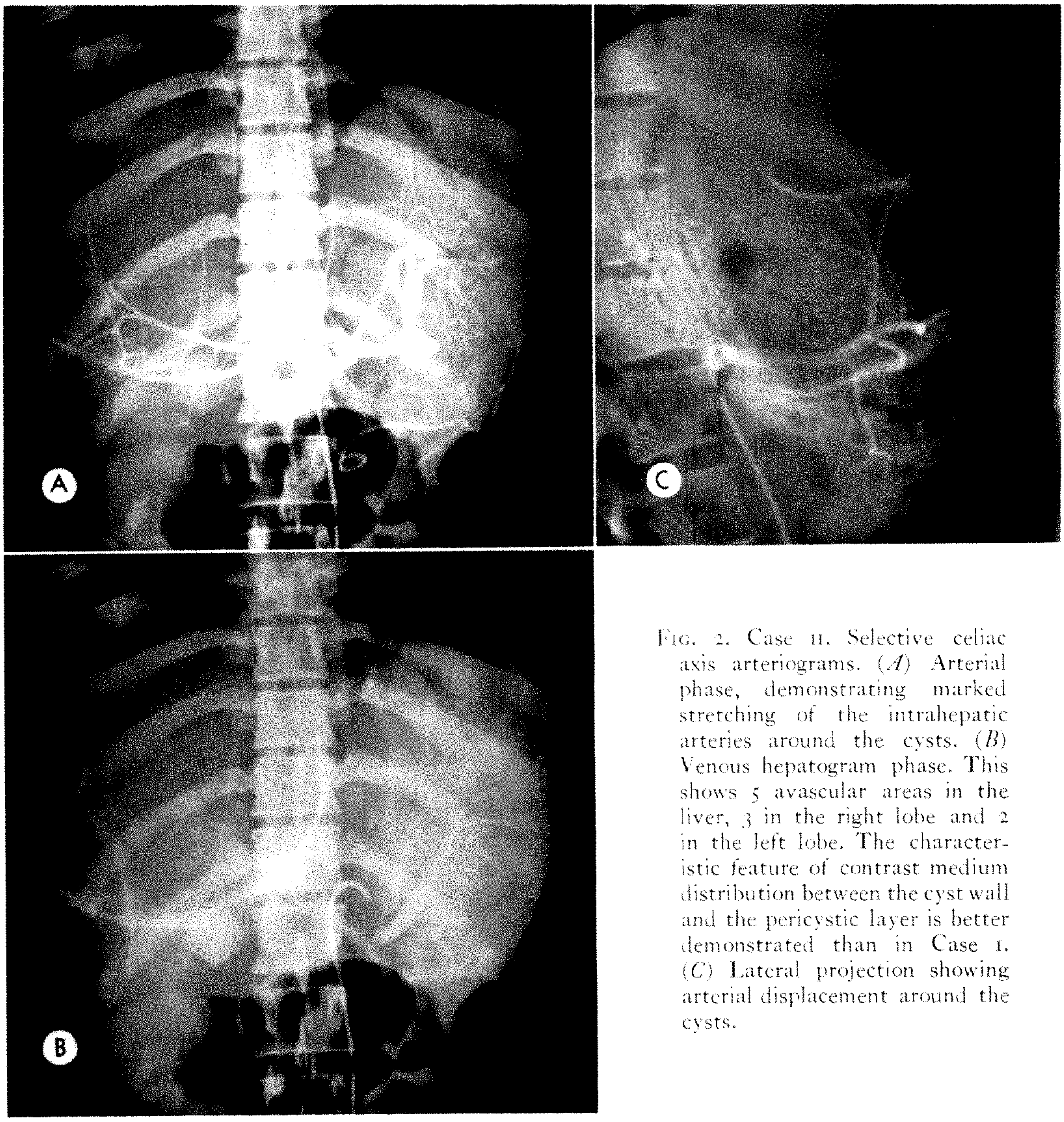

Fig. 2. Case II. Selective celiac axis arteriograms. (*A*) Arterial phase, demonstrating marked stretching of the intrahepatic arteries around the cysts. (*B*) Venous hepatogram phase. This shows 5 avascular areas in the liver, 3 in the right lobe and 2 in the left lobe. The characteristic feature of contrast medium distribution between the cyst wall and the pericystic layer is better demonstrated than in Case I. (*C*) Lateral projection showing arterial displacement around the cysts.

retention cysts may present as avascular areas at arteriography. These are generally located on the antero-inferior aspect of the right lobe of the liver.[4]

(6) Liver abscess. Both pyogenic and amebic abscess may present as an avascular area in the liver. The wall of the abscess may be opacified during the hepatogram phase due to the increased blood supply.[3] The abscess wall is usually thicker and less regular than that found in hydatid disease. The arteriographic appearances of chronic liver abscess may mimic closely a necrotic tumor, as in other areas of the body such as the kidney and brain. The history and clinical findings will usually differentiate the two possibilities.

(7) Hepatic metastases, while usually exhibiting pathologic vessels, may present as avascular areas if the tumor outgrows its blood supply and

central necrosis occurs. Hepatic metastases from adenocarcinoma of pancreas, lung, gallbladder and esophagus were noted to be avascular by Nebesar, Pollard and Stone.[12]

(8) Hydatid cysts. A solitary hydatid cyst may mimic any of the conditions listed, and if contrast medium is not seen between the cyst membrane and the pericystic layer during the hepatogram phase of the examination, it may not be possible to confirm the diagnosis at arteriography. With multiple hydatid cysts, the hepatogram phase of the examination is diagnostic and distinguishes the condition from polycystic disease of the liver.

SUMMARY

The diagnostic features of multiple hydatid cysts of the liver at selective arteriography are described. Two cases were examined by selective celiac axis and superior mesenteric arteriography. Multiple hydatid cysts in the liver produce stretching and elongation of the intrahepatic arteries in the arterial phase, and avascular areas in the hepatogram. Contrast medium distribution between the cyst wall and the pericystic layer in the venous hepatogram phase distinguishes the hydatid cysts from other causes of avascular areas in the liver at arteriography. The differential diagnosis includes: congenital polycystic disease of the liver, avascular metastatic deposits, hematoma of the liver, post-traumatic liver cysts, solitary nonparasitic cysts and pyogenic and amebic liver abscesses.

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AN ANGIOGRAPHIC SIGN DEMONSTRATING EXTENSION OF RENAL CARCINOMA INTO THE RENAL VEIN AND VENA CAVA*

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CARCINOMA of the kidney is the most frequent malignancy associated with inferior vena cava occlusion.[4] While in some instances the occlusion is non-neoplastic, the great majority of vena caval obstructions with hypernephromas are actually tumor thrombi. The usual mechanism is extension of tumor from an involved renal vein into the lumen of the inferior vena cava. Occasionally, the vena cava is invaded directly by a renal carcinoma.[5]

With the advent of renal angiography, the diagnosis of renal carcinoma has been made a relatively simple and an extremely accurate procedure. Even the diagnosis of renal vein occlusion may be inferred angiographically by observing failure of opacification of the renal vein or by visualizing venous collateral channels.[1] Involvement of the inferior vena cava is verified, as a rule, by vena cavagraphy.

Recently we have seen 6 cases of carcinoma of the kidney massively extending into the renal vein and inferior vena cava. In 5 of them an unusual striated vascular pattern was noted on selective renal angiography and we believe that this is a sign indicating the extension of renal carcinoma into the renal vein and vena cava.

REPORT OF CASES

CASE I. D.U. 2054502, a 46 year old white male entered the Boston City Hospital complaining of weight loss and fullness in the abdomen. Physical examination revealed a huge right flank mass. Urinalysis disclosed microscopic hematuria.

Intravenous pyelography: (Fig. 1*A*)—a large mass in association with a poorly functioning kidney was seen.

Renal angiography: (Fig. 1*B*)—there was a huge vascular neoplasm of the right kidney with no filling of the renal vein during the venous phase. A striated pattern of vessels located over the upper pole of the kidney at the level of the renal vein was noted. This pattern was better visualized when angiography was performed after 10 μg. of epinephrine was injected into the renal artery. These vessels appeared in the arterial filling phase and persisted through the capillary and venous phase of the angiogram.

Inferior vena cavagraphy: (Fig. 1*C*)—complete obstruction of the vena cava was seen.

Surgery: At surgery, a huge hypernephroma was found completely obstructing the renal vein with associated tumor thrombus in the vena cava.

CASE II. I.W. 2052184, a 70 year old white female entered the Boston City Hospital complaining of weight loss and a fullness in the abdomen. On physical examination a large right upper abdominal mass was palpated. Urine examination showed grossly bloody urine.

Intravenous pyelography: (Fig. 2*A*)—although the right kidney showed good function, a 10 cm. mass with distortion of the collecting system was seen in the lower pole.

Renal angiography: (Fig. 2*B*)—there was a large vascular neoplasm occupying most of the lower pole of the right kidney. A striated vessel pattern at the upper pole, renal vein level, similar to the first case was observed. This was seen more clearly when arteriography was performed after the injection of 10 μg. of epinephrine (Fig. 2*C*). There was no visualization of the renal vein in spite of the large volume of contrast material (20 cc.) injected into the renal artery.

Inferior vena cavagraphy: (Fig. 2*D*)—a huge tumor thrombus was seen, occupying the

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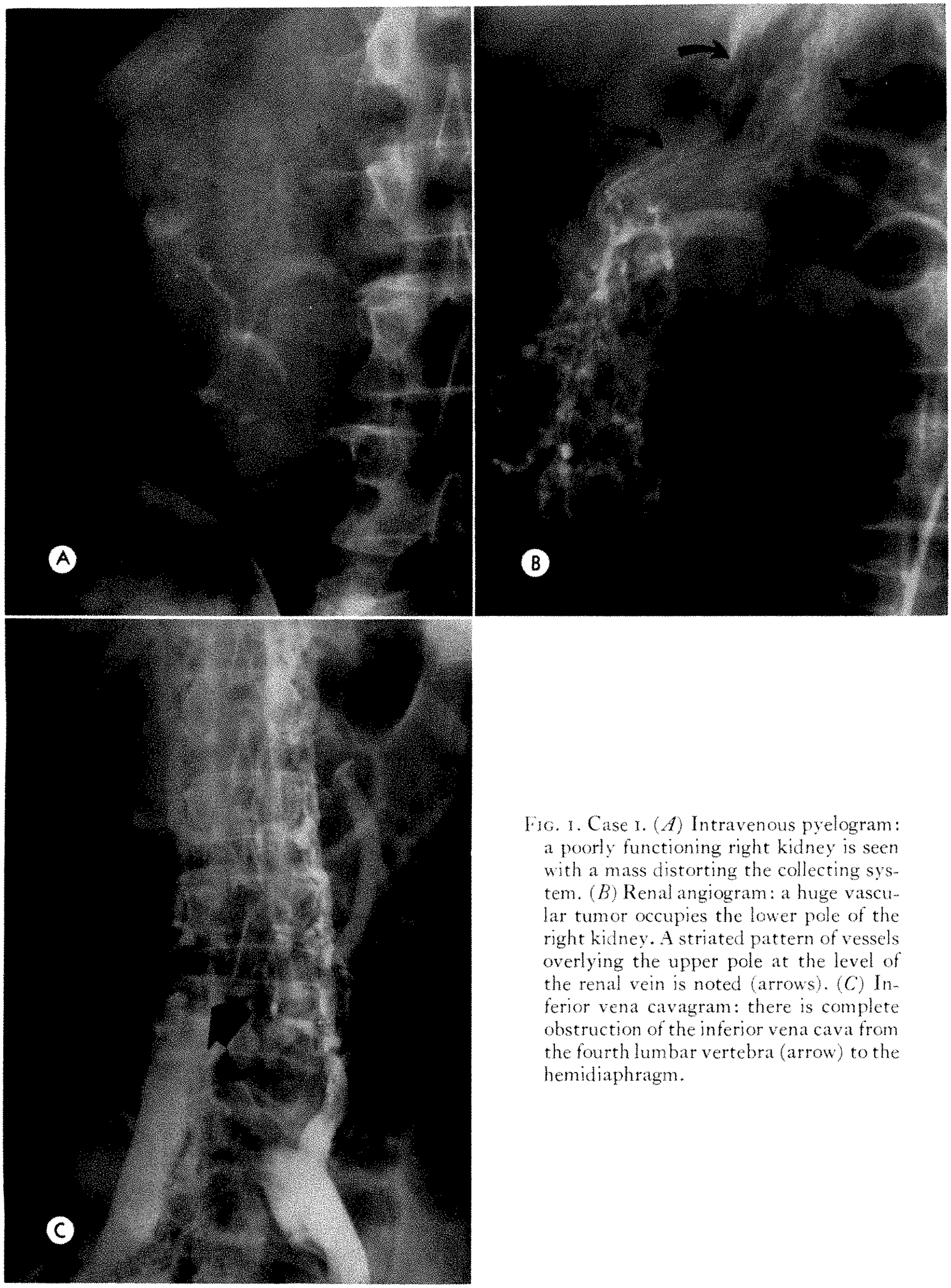

Fig. 1. Case 1. (*A*) Intravenous pyelogram: a poorly functioning right kidney is seen with a mass distorting the collecting system. (*B*) Renal angiogram: a huge vascular tumor occupies the lower pole of the right kidney. A striated pattern of vessels overlying the upper pole at the level of the renal vein is noted (arrows). (*C*) Inferior vena cavagram: there is complete obstruction of the inferior vena cava from the fourth lumbar vertebra (arrow) to the hemidiaphragm.

FIG. 2. Case II. (*A*) Intravenous pyelogram: there is gross distortion of the collecting system with a large mass occupying the mid and lower third of the kidney. (*B*) Renal angiogram: the vascular renal tumor is well seen. The striated vessel pattern as in Case I is shown by arrows. (*C*) Renal angiogram: after 10 μg. of epinephrine has been injected into the renal artery, the striated vessel pattern is seen more clearly (arrows). (*D*) Inferior vena cavagram: a huge tumor thrombus (arrows) is seen extending up to the right atrium.

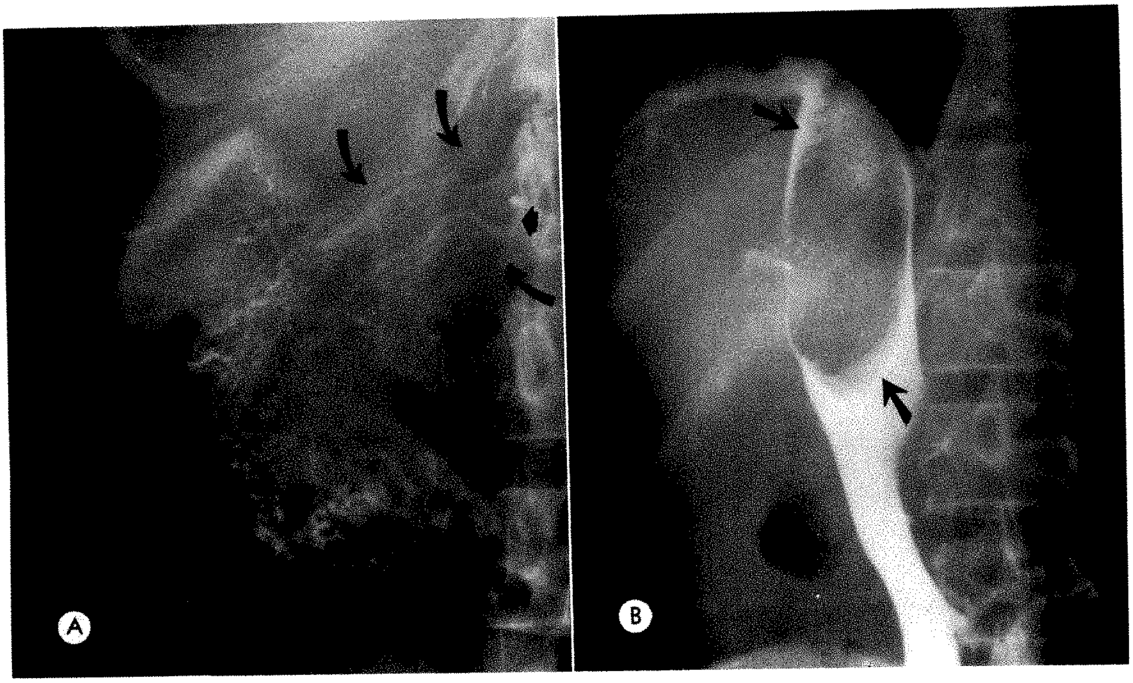

Fig. 3. Case iii. (*A*) Renal angiogram: there is a vascular tumor occupying the central portion of the kidney. The striated vessel pattern (large black arrows) is not as well seen as in the first 2 cases. A lumbar artery (short arrow) lies behind the striated vessels. (*B*) Inferior vena cavagram: caval tumor thrombus (arrows) extends from the renal vein up to the right atrium.

mid and upper third of the vena cava, and extending up to the level of the right atrium.

Due to the patient's poor general clinical status, surgery could not be performed and she died in 3 weeks. Postmortem examination was not obtained.

Case iii. G.J. 60369, a 66 year old white male entered University Hospital with gross hematuria. Physical examination disclosed a right flank mass.

Intravenous pyelography:—the collecting system of the right kidney was not visualized.

Renal angiography: (Fig. 3*A*)—a vascular tumor of the kidney with absence of filling of the renal vein was detected. The striated vessel pattern in the region of the renal vein and vena cava was noted although not as clearly as in the first 2 patients. This may be related to the poor quality of the angiogram in this case.

Inferior vena cavagraphy: (Fig. 3*B*)—a huge thrombus was present in the vena cava extending from the level of the renal veins up to the right atrial junction.

Surgery: A huge hypernephroma with tumor thrombus filling the renal vein and vena cava was partially resected. The renal capsule and perirenal fat were both invaded with tumor.

Case iv. S.A. 2038102, a 46 year old white male entered the Boston City Hospital with hematuria. A mass in the left flank was felt on physical examination.

Intravenous pyelography: (Fig. 4*A*)—there was function of the left kidney. A lower pole mass with amputation of the middle and lower calyces was seen.

Renal angiography: (Fig. 4*B*)—a vascular tumor almost completely replacing the mid and lower portion of the left kidney was demonstrated. There was no filling of the renal vein. At the renal vein level, a linear striated pattern was seen.

Inferior vena cavagraphy: (Fig. 4*C*)—the vena cava was occluded at the level of the left renal vein. The thrombus extended up to the right atrium.

Surgery: A radical left nephrectomy for hypernephroma of the kidney was performed. There was extension of tumor thrombus into the renal vein and vena cava.

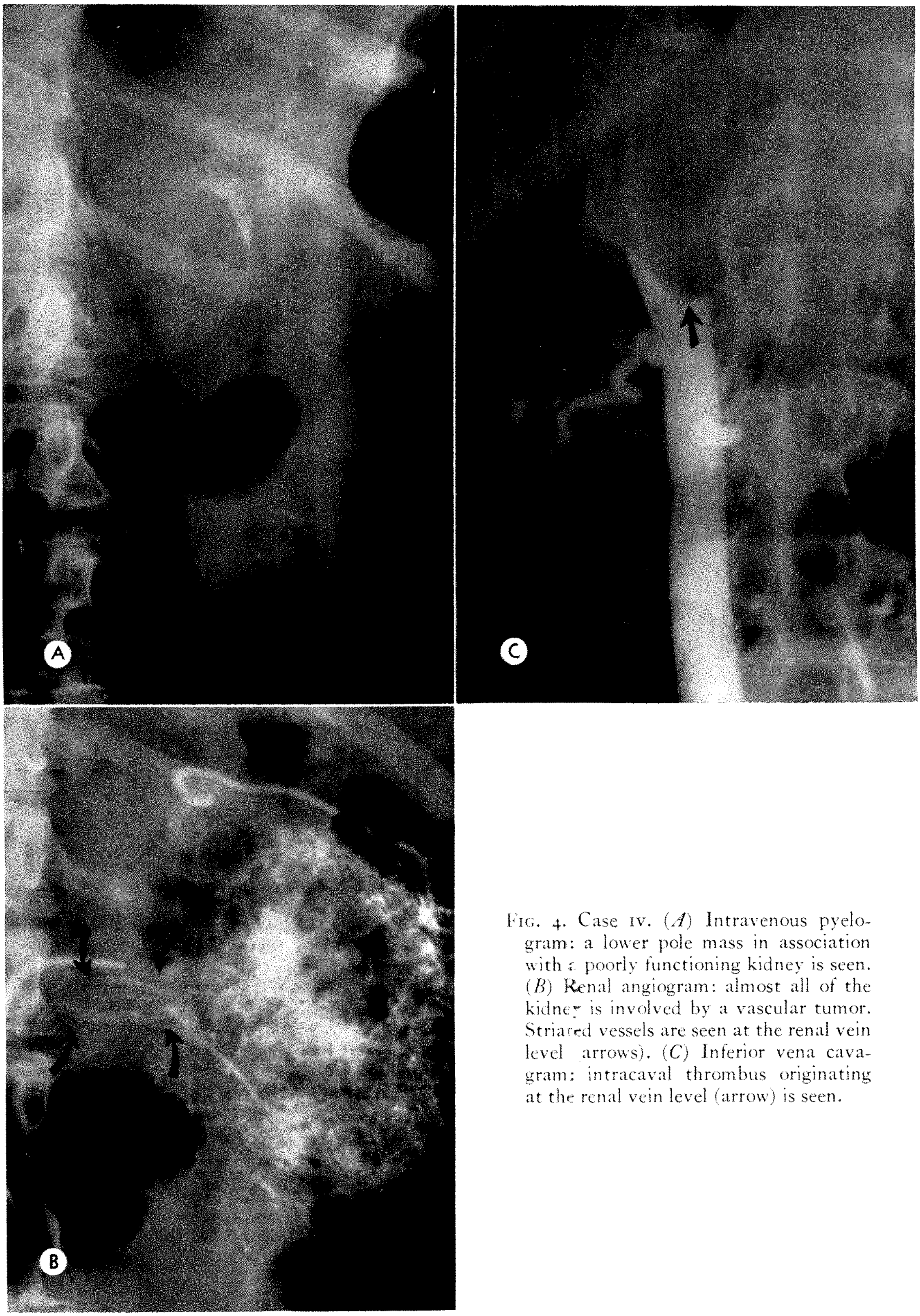

Fig. 4. Case iv. (*A*) Intravenous pyelogram: a lower pole mass in association with a poorly functioning kidney is seen. (*B*) Renal angiogram: almost all of the kidney is involved by a vascular tumor. Striated vessels are seen at the renal vein level (arrows). (*C*) Inferior vena cavagram: intracaval thrombus originating at the renal vein level (arrow) is seen.

Case v. W.B. 2038870, a 60 year old white male entered the Boston City Hospital with hematuria. Physical examination disclosed a right flank mass.

Intravenous pyelography: (Fig. 5*A*)—there was no function of the right kidney. The renal contour was lobulated and the lower pole bulbous.

Renal angiography: (Fig. 5*B*)—a vascular neoplasm was seen. On the delayed roentgenograms, the renal vein was not visualized.

Inferior vena cavagraphy: (Fig. 5*C*)—a huge thrombus of the vena cava almost completely obstructing the lumen was seen.

Surgery: At operation it was verified that the hypernephroma had extended into the renal vein and inferior vena cava.

Case vi. L.B. 2079852, a 48 year old white female entered the Boston City Hospital with hematuria and anasarca. Physical examination showed massive ascites.

Intravenous pyelography: There was a faint concentration of contrast material present in the upper collecting system.

Renal angiography: (Fig. 6*A*)—a huge vascular tumor of the left kidney was apparent. A linear confined pattern of vessels conforming to the position and contour of the left renal vein and vena cava was seen (arrows).

Inferior vena cavagraphy: (Fig. 6*B*)—a huge tumor thrombus was seen in the vena cava. The vessels to the right of the spine on the renal angiogram (Fig. 6*A*) correspond to the contour and location of the defect in the vena cava.
Comment: This is essentially a more definitive demonstration of Case iv.

DISCUSSION

Ney[5] found that 35 of 51 cases of vena caval occlusion secondary to renal carcinoma originated from the right renal vein, perhaps due to its shorter length. In our cases, 4 were on the right and 2 on the left side.

The diagnosis of renal vein occlusion with a hypernephroma is suggested by a nonfunctioning kidney on intravenous pyelography.[3] According to Boijsen and Folin,[1] if 10 cc. or more of contrast material is used in selective renal angiography, the renal vein should be opacified on the venous phase of the study. It follows therefore that failure of opacification of the renal vein under these circumstances may indicate that either intraluminal obstruction or extrinsic compression of the renal vein has occurred.

The linear striated vessel pattern noted in the renal angiogram appeared to be confined to the anatomic position of the renal vein and vena cava in each case. Verification of tumor thrombus in the renal vein and vena cava conforming to this striated pattern was made roentgenographically or surgically. We therefore believe that the striated pattern of vessel flow demonstrated in this report is due to supply of the intraluminal tumor by vessels originating in the kidney. This correlates with a case demonstrated by Kahn,[2] who in presenting material on the epinephrine effect in selective renal angiography demonstrated a case identical to Case iv in our series. He believed that the pattern represented "tumor vessels" supplying tumor in the renal vein. This was confirmed at surgery to be within tumor growing along the renal vein into the inferior vena cava.

This vascular striated pattern was best demonstrated when epinephrine in the doses of 10 μg. had been used prior to angiography in order to better study the renal neoplasm. The use of epinephrine decreased flow into normal vessels and directed most of the contrast material into "tumor vessels." We suspect that with the more widespread use of epinephrine in renal angiography, better delineation of the blood supply of renal vein and vena caval tumor extension will be more frequently seen.

The reason for visualization of the kidney on intravenous pyelography in 4 of the cases, even with extensive tumor involvement of the renal vein, is not clear. Collateral circulation was not seen in any of the cases. Possibly the tumor thrombus did not completely occlude the lumen of the vein and also possibly some drainage of the kidney was facilitated by the increased

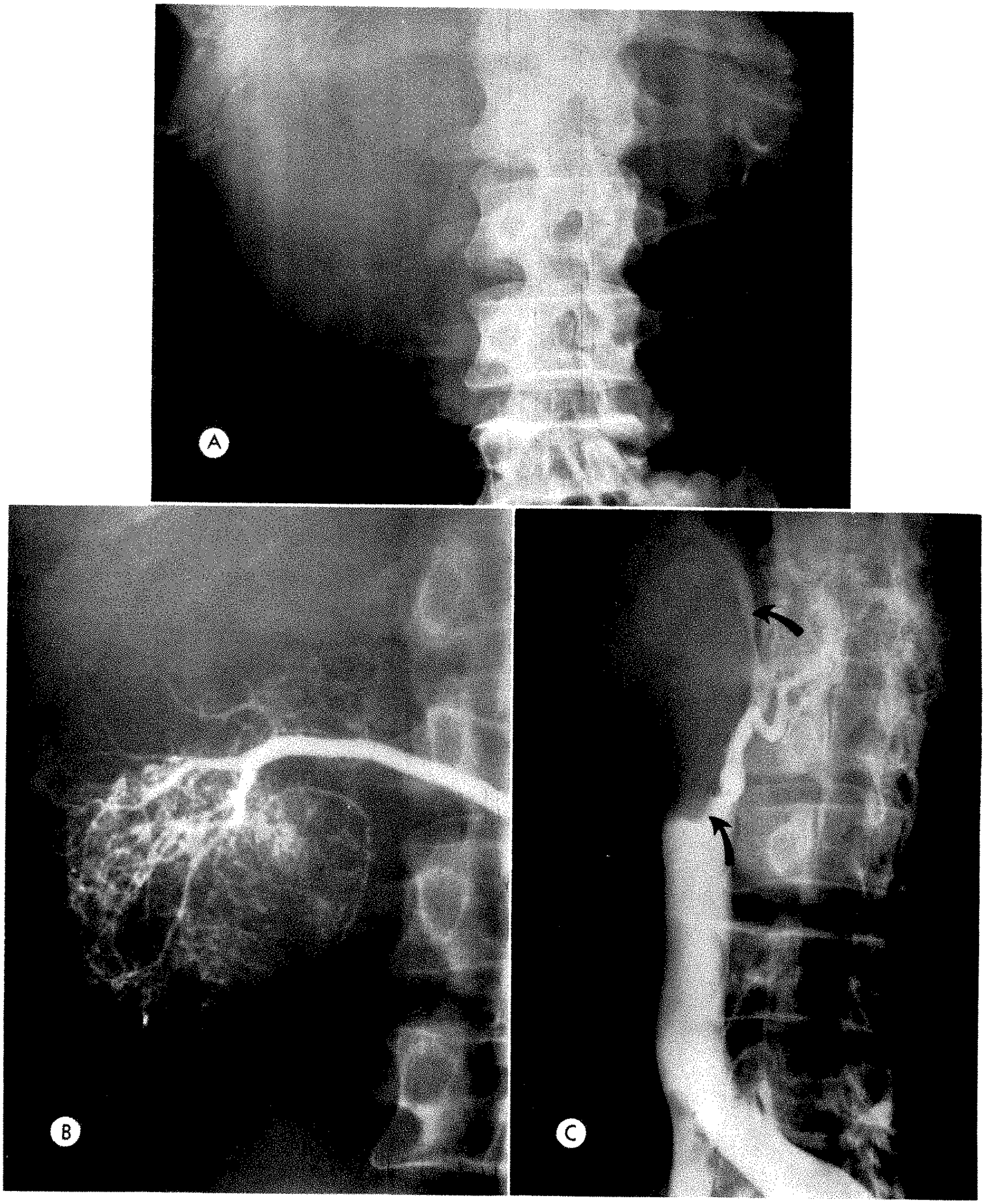

FIG. 5. Case v. (*A*) Intravenous pyelogram: there is no function of the right kidney. The renal outline is bulbous. (*B*) Renal angiogram: the kidney has almost been completely replaced by a massive vascular hypernephroma. No striated pattern of vessels was seen in this case. (*C*) Inferior vena cavagram: a huge thrombus almost completely obstructs the inferior vena cava (arrows).

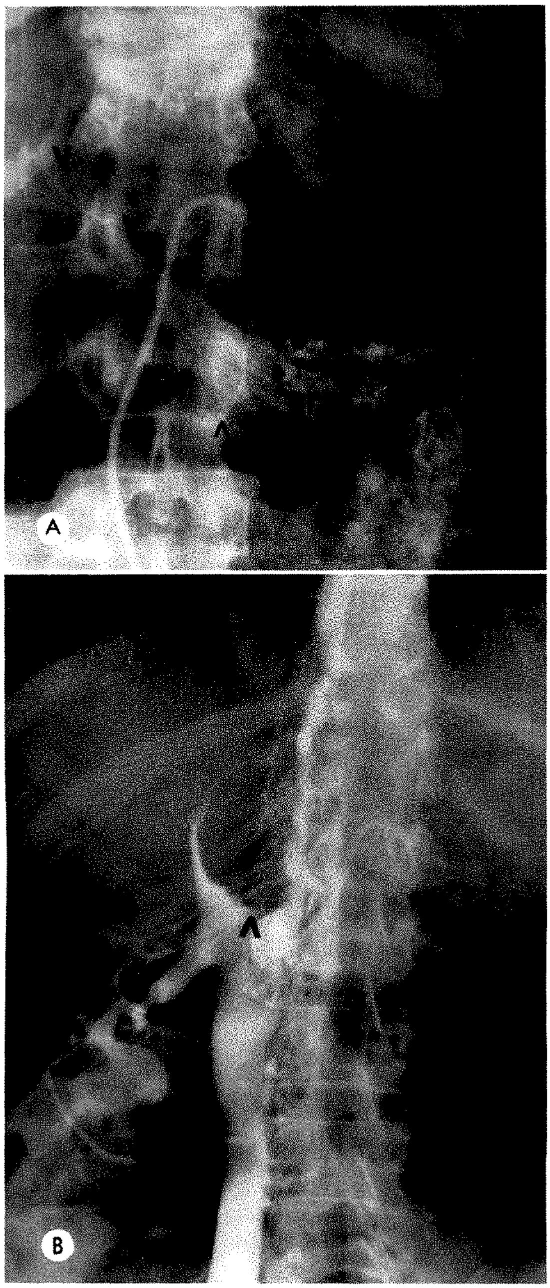

Fig. 6. Case vi. (*A*) Left selective renal angiogram in the capillary phase shows a tubular confined pattern of vessels (arrows) corresponding to the position and contour of the renal vein and vena cava. (*B*) Inferior vena cava study illustrates a huge filling defect in the vena cava with obstruction (arrow). The vessels, seen on the angiogram to the right of the spine in *A*, can be superimposed over the tumor thrombus on the vena cava study.

blood flow to the intracaval tumor. It is interesting to note that nonvisualization on intravenous pyelography occurred in the one case in which the striated vessel pattern was not seen and in another in which the pattern was poorly seen.

Another possible explanation for the striated vessel pattern was considered. This was opacification of collateral venous drainage (to the azygos system via adrenal veins). However, on the basis of pathologic-roentgenologic correlation in these cases, we feel this unlikely, although not completely excluded in some cases.

SUMMARY

Six cases of renal carcinoma with massive extension into the renal vein and inferior vena cava are reported. In 4 cases the right kidney was involved and in 2, the left.

A striated vascular pattern was noted on renal angiography in 5 of the 6 cases. The pattern was particularly well seen when epinephrine had been used as a part of the angiographic study. It is believed that this striated vessel pattern represents vascular supply of tumor extension confined to the renal vein and vena cava.

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THE COLLATERAL ARTERIAL CIRCULATION IN THE PELVIS*

AN ANGIOGRAPHIC STUDY

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THE collateral arterial circulation in the pelvis has been described in remarkable detail by the classical anatomists, without benefit of angiography or injection-corrosion techniques.[3] These collateral channels have been demonstrated to account for perfusion of structures distal to arteriosclerotic vascular occlusions.[2,4] In the course of ligating the internal iliac arteries and their branches in women undergoing pelvic surgery, we have noted, on postoperative angiography, that these same collateral channels function soon after surgery. Similar findings have been noted following traumatic occlusion.

MATERIAL AND METHOD

Fifteen women with carcinoma of the cervix uteri underwent ligation of major pelvic vessels, either in the course of radical hysterectomy or as a means of controlling bleeding. Two patients had a common iliac artery severed by a bullet, one child had an iatrogenic occlusion of a superficial femoral artery at cardiac catheterization, and one had numerous vascular divisions in an attempt at extirpation of an hemangioma of the buttock.

All patients were studied by means of transfemoral percutaneous catheterizations of the Seldinger type,[5] with the exception of one patient examined by means of translumbar aortography. Injections were made with the catheter tip passed into the lower abdominal aorta (the end hole being occluded in some cases). Fifty cc. of sodium diatrizoate/methylglucamine diatrizoate* were injected under a pressure of 300 pounds per square inch with the Cordis injector during filming in the frontal projection at the rate of 2 frames per second with either the Schönander or the Sanchez-Perez film changer.

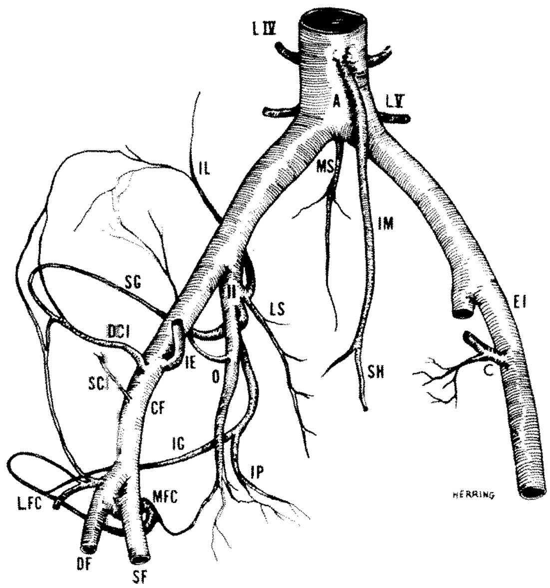

FIG. 1. Sketch of pertinent pelvic anatomy. Abbreviations in sketch and illustrative angiograms: C = common trunk of obturator and inferior epigastric arteries; CF = common femoral artery; DCI = deep iliac circumflex artery; DF = deep femoral artery; EI = external iliac artery; IE = inferior epigastric artery; IG = inferior gluteal artery; II = internal iliac artery; IL = iliolumbar artery; IM = inferior mesenteric artery; IP = internal pudendal artery; LFC = lateral femoral circumflex artery; L-IV = fourth lumbar artery; L-V = fifth lumbar artery; LS = lateral sacral artery; MFC = medial femoral circumflex artery; MS = middle sacral artery; O(OBT) = obturator artery; PI = first perforating artery; SF = superficial femoral artery; SH = superior hemorrhoidal artery (of inferior mesenteric artery); X = point of ligation.

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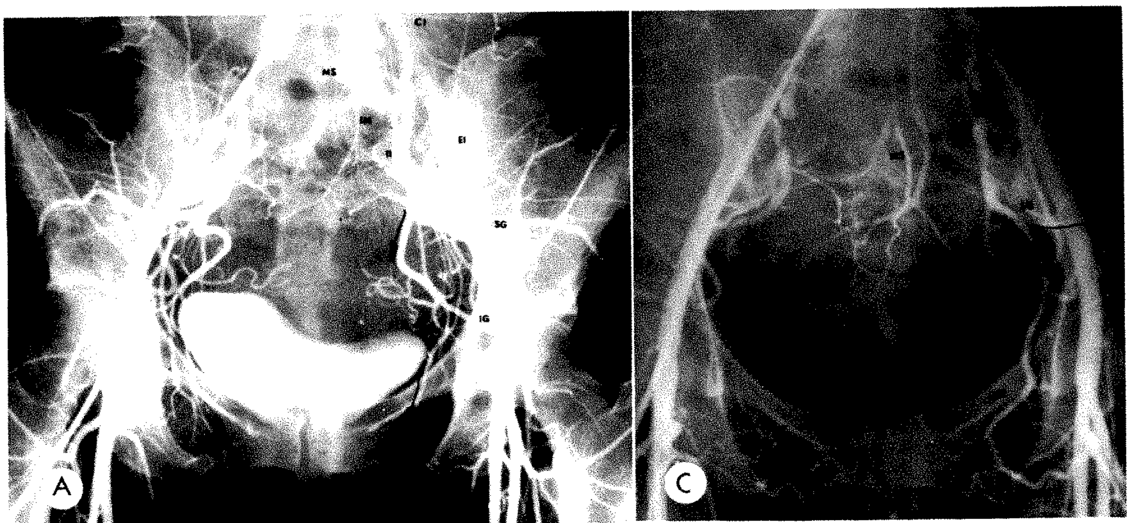
Preoperative studies were available in some cases. Serial roentgenograms were examined to determine which collateral channels accounted for flow in each case. Figure 1 is a sketch of the major pelvic arteries.

REPORT OF CASES

CASE I. R. O., a 34 year old woman, underwent a modified radical hysterectomy on August 20, 1964, for carcinoma *in situ* of the cervix. Bilateral internal iliac artery ligations were performed incident to the procedure. A preoperative pelvic arteriogram demonstrated normal flow (Fig. 2*A*). A repeat angiogram performed 8 days following surgery (Fig. 2*B*) demonstrated ligation of both internal iliac arteries. This study showed early filling of the medial femoral circumflex→obturator anastomosis and an increase in caliber of these 2 vessels, as well as of the middle sacral and inferior mesenteric arteries. One second later, (Fig. 2*C*), the entire internal iliac artery was seen to be filled.

CASE II. L. K., a 49 year old woman, underwent radiation therapy in November 1963 for a Stage IV carcinoma of the cervix. Bilateral ligations of the internal iliac, uterine, superior vesical and vaginal arteries were performed on May 31, 1964 to control bleeding. Angiography was performed approximately 3 weeks later. An angiogram made 1.5 seconds following onset of injection demonstrated ligation of both internal iliac arteries with sparing of the iliolumbar arteries (Fig. 3*A*). The middle sacral artery was larger than normal and flow occurred in a



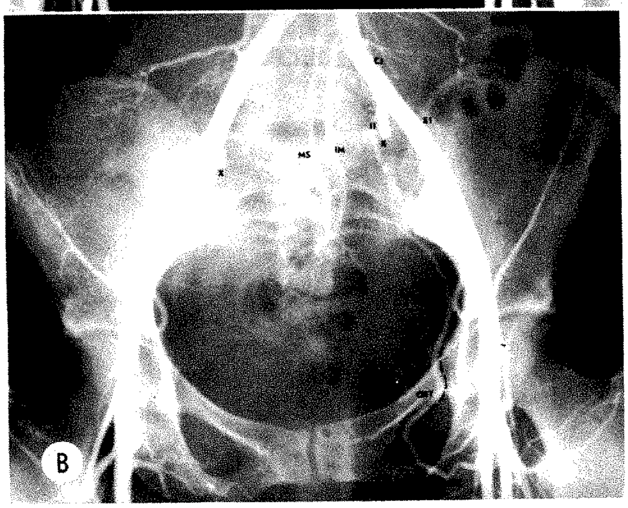


FIG. 2. Case I. (*A*) Preoperative pelvic arteriogram demonstrating normal anatomy. (*B*) Postoperative angiogram taken 1 second after onset of injection. Both internal iliac arteries have been ligated at "X." Filling is seen at this early stage in the medial femoral circumflex obturator anastomosis. There is increased caliber of these vessels and of the middle sacral and inferior mesenteric arteries. (*C*) Angiogram 1 second later shows complete filling of both internal iliac arteries and their branches. In all illustrations the unbroken arrowed lines indicate flow in normal antegrade direction. The broken arrowed lines indicate retrograde flow in response to altered hemodynamics.

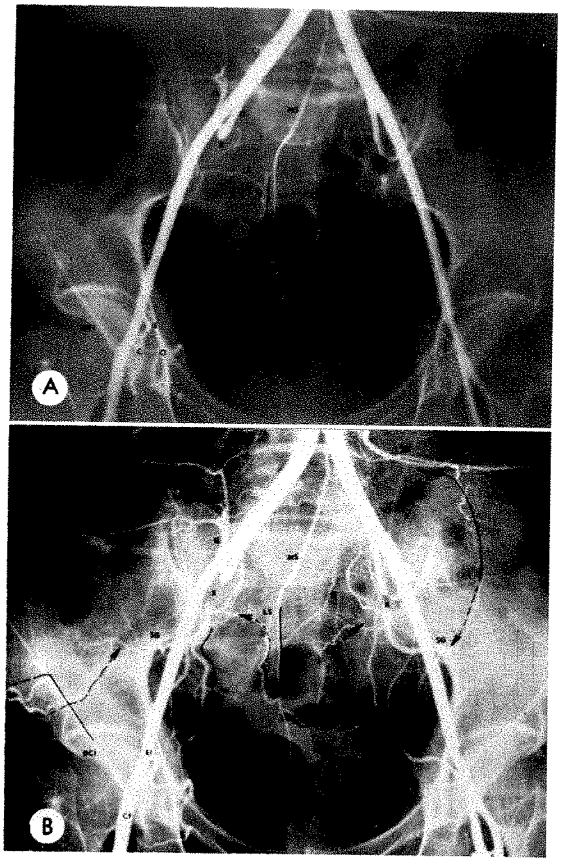


Fig. 3. Case II. (*A*) An angiogram taken 1.5 seconds post injection shows bilateral internal iliac artery ligation at "X" with sparing of the iliolumbar arteries, widening of the middle sacral artery with retrograde filling from the middle sacral to the lateral sacrals. A common trunk of the right inferior epigastric and obturator arteries is present. (*B*) Angiogram 1 second later shows additional filling of right internal iliac artery via a functioning anastomosis between the deep iliac circumflex and superior gluteal arteries.

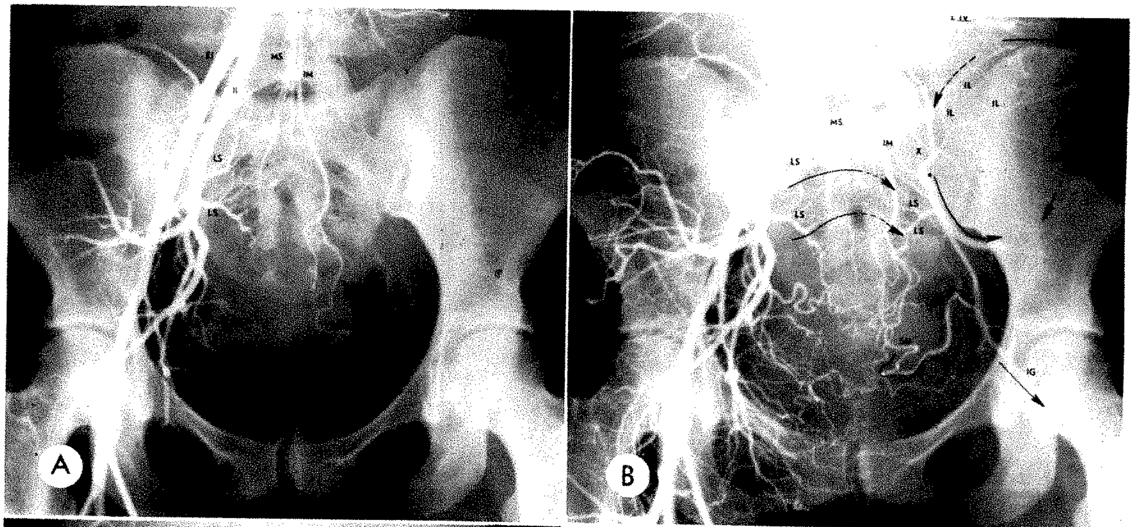
retrograde fashion from the middle sacral to the lateral sacral arteries with filling of the internal iliac arteries. A frequent variant, a common trunk of the inferior epigastric and obturator arteries was present on the right. An angiogram made 1 second later (Fig. 3*B*) showed a functioning anastomosis between the deep circumflex iliac artery and the superior gluteal artery on the right. On the left, flow from the last lumbar artery aided filling of the superior gluteal artery.

Case III. C. R., a 39 year old woman, underwent a radical hysterectomy with bilateral internal iliac artery ligation for Stage I carcinoma of the cervix in October 1963. Arteriography was performed in June 1964. A film exposed 1 second following the onset of injection (Fig. 4*A*) demonstrated catheter dissection of the right external and common iliac arteries. A wide area of lucency visible between the opacified catheter and the contrast material within the right common iliac artery represented dissected intima. Flow in the iliac arteries on this side was poor as a result. On this arteriogram both iliolumbar arteries can be seen to fill in retrograde fashion through the last lumbar arteries. The middle sacral artery was enlarged in caliber. Arteriogram (Fig. 4*B*) made 1 second later, demonstrated further filling of the internal iliac arteries via the middle→lateral sacral artery anastomoses. On the left, the medial femoral circumflex→obturator artery anastomosis added to the internal iliac artery filling. On the right, however, because of nonfilling of the external iliac artery, the direction of flow was obturator→medial femoral circumflex artery maintaining flow in the femoral artery.

In an attempt to assess the damage to the right external and common iliac arteries, the catheter was removed from the right side and passed percutaneously through the left femoral artery to a point above the iliac bifurcation. Arteriogram (Fig. 4*C*) made 2 seconds following the onset of injection, showed nonfilling of either external or common iliac artery. This was probably due to intimal damage by the catheter and spasm on the right, and to spasm alone on the left. On the right, the femoral artery continued to fill via the last lumbar→iliolumbar→internal iliac→obturator→medial femoral circumflex collateral system. This same series of anastomoses now functions on the left as well, representing a reversal of medial femoral circumflex→obturator flow demonstrated in Figure 4*B*.

One week later, an intravenous pelvic arteriogram (Fig 4*D*) demonstrated the situation on the right to be unchanged. There still appeared to be complete occlusion of the distal portion of the right external iliac artery with peripheral perfusion accomplished via the aforementioned anastomoses. On the left, spasm had relented and the anastomoses demonstrated in Figure 4*B* now function. The patient was asymptomatic throughout this period and had equal and adequate femoral pulses.

FIG. 4. Case III. (*A*) Arteriogram made 1 second after onset of injection shows catheter dissection of the right external and common iliac arteries with resultant poor flow. The iliolumbar arteries fill via the last lumbar arteries. (*B*) One second later there is further filling of both internal iliac arteries via the middle sacral →lateral sacral anastomoses. On the left, the middle femoral circumflex→obturator anastomosis adds to internal iliac filling. On the right, however, because of nonfilling of the external iliac arteries, the direction is obturator→medial femoral circumflex, thus maintaining flow in the femoral arteries. (*C*) In an attempt to assess the damage to the right external and common iliac arteries, the catheter was removed from the right side and passed through the left femoral artery to above the iliac bifurcation. This film exposed 2 seconds after injection shows nonfilling of either external iliac–common iliac system. On the right side this is probably due to intimal damage by the catheter plus spasm and on the left to spasm alone. Now both femoral arteries fill via the last lumbar→iliolumbar→internal iliac→obturator→medial femoral circumflex collaterals. Note that this constitutes a reversal of flow in the obturator→medial femoral circumflex on both sides as compared with the normal. (*D*) An intravenous pelvic arteriogram made 1 week later shows that the situation on the right is unchanged, with the spasm on the left having relented. The patient was asymptomatic throughout with palpable pulses bilaterally.



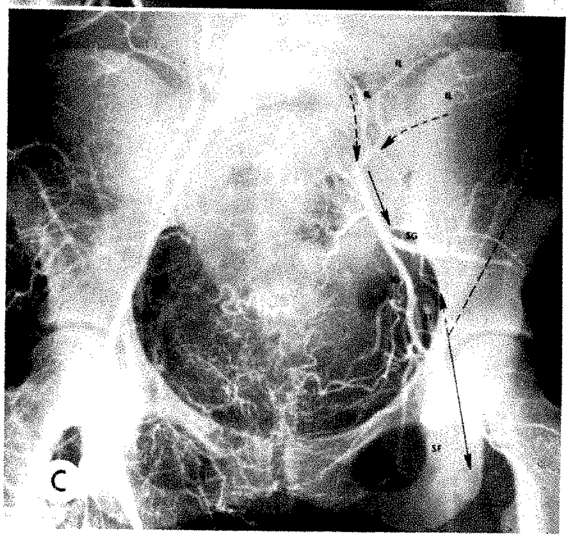


FIG. 5. Case IV. (*A*) This study was performed after end-to-end anastomosis of a traumatically severed left common iliac artery. An angiogram taken 1 second after onset of injection demonstrates spontaneous occlusion of the anastomosis with nonfilling of the left iliac artery. (*B*) A film exposed 2 seconds following the onset of injection shows left internal iliac artery filling via the right lateral sacral→left lateral sacral, last lumbar →iliolumbar collaterals. Particularly well shown is the superior hemorrhoidal (inferior mesenteric) →middle hemorrhoidal anastomosis. Note filling of the deep iliac circumflex artery via the last lumbar→iliolumbar twigs. (*C*) Four seconds after onset of injection the left internal iliac branches are well filled via the above mentioned anastomoses. In addition, the external iliac and femoral arteries are faintly opacified via the deep iliac circumflex artery.

CASE IV. A. J., a 29 year old woman, sustained a gunshot wound of the abdomen. Exploration revealed complete severance of the left common iliac artery. An end-to-end anastomosis was performed. Subsequently, left sided pulses diminished in amplitude, although they remained faintly palpable. An angiogram, made 1 second following injection demonstrated nonfilling of the left pelvic vessels (Fig. 5*A*). The inferior mesenteric artery with its superior hemorrhoidal branch, and the last lumbar artery on the left were enlarged in caliber. An angiogram (Fig. 5*B*) made 1 second later, demonstrated filling of the internal iliac artery on the left via several collateral routes: the right lateral sacral artery flowed into the left lateral sacral artery; the last lumbar artery on the left anastomosed with the iliolumbar artery; the superior hemorrhoidal artery, a branch of the inferior mesenteric artery, filled the middle hemorrhoidal artery; the deep circumflex iliac artery was faintly opacified via last lumbar→iliolumbar anastomoses. In an arteriogram, made 2 seconds later (Fig. 5*C*), the internal iliac artery branches were seen to be well filled via the anastomoses named above. The external iliac artery and the femoral artery were faintly opacified via the deep circumflex iliac artery.

CASE V. H. M., a 49 year old woman, underwent radiation therapy for carcinoma of the

cervix, Stage IV in July 1963. Bilateral internal iliac artery ligation was performed in March, 1964 to control bleeding. Arteriography was performed 28 days later. A film exposed, 1 second following the onset of injection (Fig. 6*A*) demonstrated bilateral ligation of the common trunks of the internal iliac arteries. The middle sacral artery was enlarged in diameter. There was a common origin of the inferior epigastric and obturator arteries on the right. The inferior epigastric and obturator arteries arose independently on the left. Filling of the left obturator artery in a direction opposite that of normal flow occurred via the medial femoral circumflex→obturator anastomosis. An arteriogram made 1 second later (Fig. 6*B*) demonstrated, on the right, filling of the inferior gluteal artery via a lateral branch of the medial femoral circumflex artery and filling of the lateral sacral arteries in a direction opposite normal flow via anastomoses with the middle sacral artery. On the left, there was further filling of the obturator artery via a medial branch of the medial femoral circumflex artery, and filling of the superior gluteal artery via the lateral femoral circumflex arteries.

Case VI. D. G., a 9 year old girl, entered the hospital with an hemangioma of the buttock. A preoperative angiogram (Fig. 7*A*) demonstrated abnormal pooling of contrast material in the soft tissue of the left buttock. The hemangioma appeared to be fed predominantly by the inferior gluteal artery. In an attempt to diminish perfusion of this lesion prior to surgical removal, the internal iliac artery was divided at its origin. A film exposed on the operating table immediately following division (Fig. 7*B*) demonstrated that the hemangioma continued to fill well via this same inferior gluteal artery. The anastomoses which accounted for filling of this vessel could not be identified since this surgical angiogram was not made with serial filming. However, the lateral femoral circumflex artery had increased in caliber as compared with Figure 7*A* and appeared to perfuse the lesion. At this time, the last lumbar artery, the medial and lateral femoral circumflex arteries, and the middle sacral artery were all divided. A second opera-

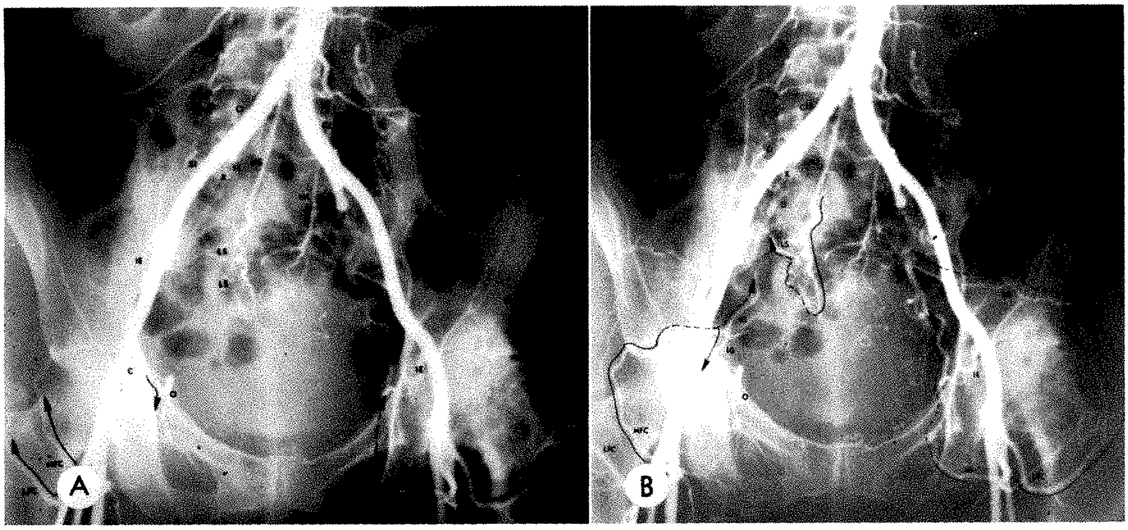


Fig. 6. Case v. (*A*) Arteriogram made 1 second following the onset of injection, demonstrates bilateral ligation of the common trunks of the internal iliac arteries at "X," an increase in diameter of the middle sacral artery and a common origin of the inferior epigastric and obturator arteries on the right (a frequent anatomic variation). Filling of the left obturator artery occurs in a direction opposite that of normal flow via the medial femoral circumflex→obturator anastomosis. (*B*) Arteriogram made 3 seconds after the onset of injection demonstrates on the right that there is filling of the inferior gluteal artery via lateral branch of the medial femoral circumflex artery and that filling of the lateral sacral arteries is in a direction opposite that of normal flow via anastomoses with the middle sacral artery. On the left, there is further filling of the obturator artery via the medial branch of the medial femoral circumflex artery. In addition, there is filling of the left superior gluteal artery via reverse flow from the lateral femoral circumflex artery.

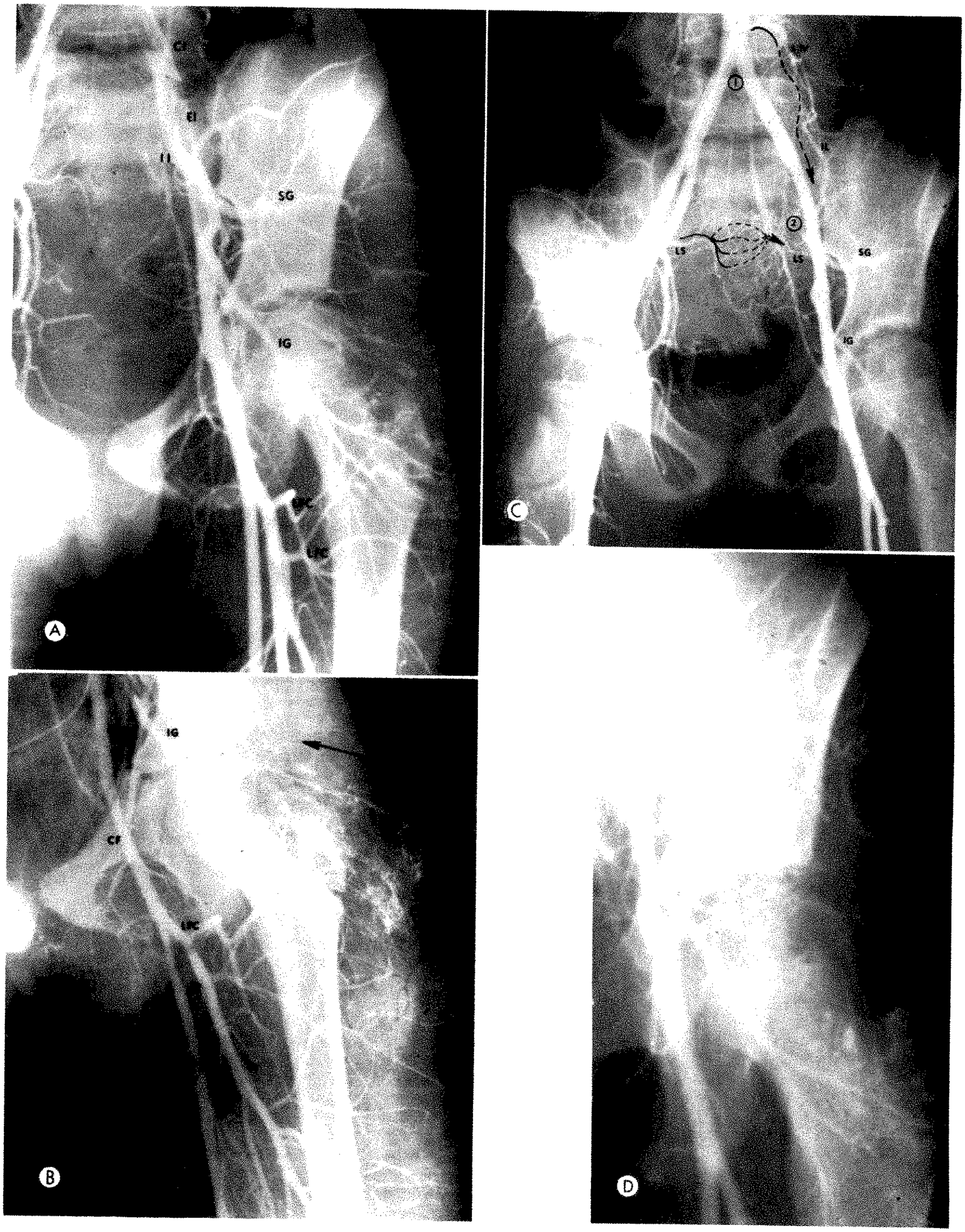


FIG. 7. Case VI. (*A*) This preoperative angiogram demonstrates normal anatomy and pooling of contrast material in the soft tissues of the left buttock, representing an hemangioma fed predominantly by the inferior gluteal artery. (*B*) An operative angiogram made immediately after division of the left internal iliac artery in an attempt to diminish the blood supply of the lesion. The hemangioma continues to fill well via the inferior gluteal artery as before ligation. The anastomoses filling the internal iliac artery are not identified; however, there is increased caliber of the lateral femoral circumflex artery which is probably now a major

tive angiogram demonstrated continued perfusion of the lesion. Further surgical intervention was abandoned. A pelvic angiogram (Fig. 7*C*) made 1 week following surgery demonstrated filling of the left iliolumbar artery via the fourth lumbar artery. The left lateral sacral arteries filled via the right lateral sacral arteries. Branches of the internal iliac artery, including the inferior gluteal artery, continued to fill. A late angiogram demonstrated continued good opacification of the hemangioma (Fig. 7*D*).

DISCUSSION

We have attempted to demonstrate the major anastomotic channels functioning following various pelvic arterial ligations and occlusions. Our demonstrations are restricted to those channels which on sequential angiograms can be shown significantly to contribute to flow; we have not discussed those, which, although demonstrated, appear not to be of hemodynamic significance. We have demonstrated in Cases III and VI that these anastomoses will function *immediately* following occlusion, and also in Case VI the futility of attempting to notably decrease flow to an hemangioma in this area. In each case one main anastomotic system appears to be responsible for most of the perfusion distal to the point of ligation. The same system is not necessarily operative bilaterally in the same patient. However, measurements of blood flow and blood pressure demonstrate that internal iliac artery ligation controls pelvic hemorrhage by markedly reducing the pressure and flow in the visceral branches of the artery.[1] It is clear, nevertheless, that there is continued flow distal to ligation.

We have demonstrated, in Cases III and IV, that femoral flow may be maintained following spasm or occlusion of the external and common iliac arteries, and we suggest that such occurrences following transfemoral catheterization may be more common than suspected.

It should be emphasized that all the patients in this series were below the age of 49 years and may be assumed to have had normal arteries. No patient was hypertensive. It is not suggested that sudden occlusion of arteriosclerotic vessels would have similar results.

SUMMARY

Nineteen patients ranging in age from 9 to 49 years were subjected to pelvic angiography following internal or common iliac artery occlusion. None of those patients manifested evidence of cardiovascular disease.

Roentgenographic demonstration of the major arterial anastomoses is presented. The anastomoses shown are:

1. Last lumbar→iliolumbar
2. Lateral sacral↔lateral sacral
3. Middle sacral→lateral sacral
4. Superior hemorrhoidal→middle hemorrhoidal
5. Medial femoral circumflex→inferior gluteal
6. Medial femoral circumflex↔obturator
7. Lateral femoral circumflex→superior gluteal
8. Deep iliac circumflex→superior gluteal
9. Deep iliac circumflex→external iliac
10. Last lumbar→superior gluteal
11. Last lumbar→deep iliac circumflex
12. Iliolumbar→deep iliac circumflex.

feeding vessel. Following this angiogram, ligation of the middle sacral, fifth lumbar and medial and lateral femoral circumflex arteries failed to reduce tumor vascularity. (*C*) Pelvic angiogram 1 week after surgery demonstrates filling of the left iliolumbar artery via the fourth lumbar artery and of the left lateral sacral arteries via the right lateral sacral arteries despite division of the middle sacral artery at its origin (1). Branches of the internal iliac artery ligated at (2), including the inferior gluteal artery, fill. (*D*) The hemangioma continues to be perfused in a late arterial phase.

These anastomoses have been shown to function immediately following occlusion.

Attempts at reduction of blood flow to pelvic structures may be successful, although complete cessation of perfusion probably cannot be accomplished.

Occlusion of the external iliac artery due to trauma to the intima or to spasm may be an unrecognized complication of catheter angiography, since peripheral flow and pulse may be maintained.

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THE DEMONSTRATION OF THE MESENTERIC COLLATERAL CIRCULATION IN YOUNG PATIENTS*

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IT IS well known that in the presence of splanchnic arterial disease with vascular compromise, unless adequate circulation to the alimentary tract is established, a spectrum of disorders may occur. These disorders include weight loss, diarrhea, malabsorption, ulceration, hemorrhage, stricture formation, enteritis or colitis-like syndromes, and infarction of bowel.[2,6,14] A marginal vascular supply may lead to the syndrome of intestinal angina,[11] but a well-developed collateral system will often permit the patient to remain asymptomatic.[3,11,12]

We have recently seen cases of unusual disorders affecting the abdominal vasculature in 2 young patients who, because of extensive mesenteric collateral development, had no abdominal symptomatology. The hemodynamic alterations determined by the location of the obstructed or partially obstructed vessels is also demonstrated. As it is rare to demonstrate the mesenteric collateral system in young patients, we felt that their description would be a worthwhile contribution.

REPORT OF CASES

CASE I. J.J., a 25 year old Caucasian male, previously in good health, was first discovered to have hypertension on a routine physical examination. His childhood history was unremarkable, and he engaged in competitive team sports during his school years, and while in the military service. Hypertension was discovered while he was undergoing his discharge physical examination.

Admission physical examination revealed a blood pressure of 180/100 in his left arm and 200/110 in his right arm. Lower extremity blood pressure was 220/120. His pulse on admission was 135 beats per minute, but his pulse rate while sleeping was 80 beats per minute. Further pertinent findings were a loud systolic bruit heard over the entire precordium, right cervical area, and left suprascapular region with radiation to both infra and interscapular areas. The bruit was especially well heard over the abdomen, particularly in the left upper quadrant, and bilaterally over the costovertebral angles. During hospitalization his blood pressure was quite labile, and at times he was relatively normotensive. His thyroid function studies were normal. Because of the bruits over his chest, back, and abdomen, as well as the apparent recent onset of labile hypertension, aortography was performed.

Findings at Aortography. The first injection was performed through a catheter introduced into the ascending aorta percutaneously via the femoral artery. This revealed bilateral subclavian artery stenotic areas with pre and post-stenotic dilatations, enlarged internal mammary arteries bilaterally, and an absent left vertebral artery (Fig. 1*A*). A markedly irregular lower thoracic and upper abdominal aorta was demonstrated, but the renal arteries were of normal caliber (Fig. 1*B*). *Significantly, the celiac axis trunk and superior mesenteric artery were not filled in the expected sequence.* However, a dilated inferior mesenteric artery was observed to arc in the pelvis and proceed upward toward the left upper quadrant of the abdomen (Fig. 1, *B–D*). The arterial pathways below the origin of the inferior mesenteric artery from the aorta were normal (Fig. 1*C*). After the dilated inferior mesenteric artery

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This material has been reviewed by the Office of The Surgeon General, Department of the Army, and there is no objection to its presentation and/or publication. This review does not imply any indorsement of the opinions advanced or any recommendation of such products as may be named.
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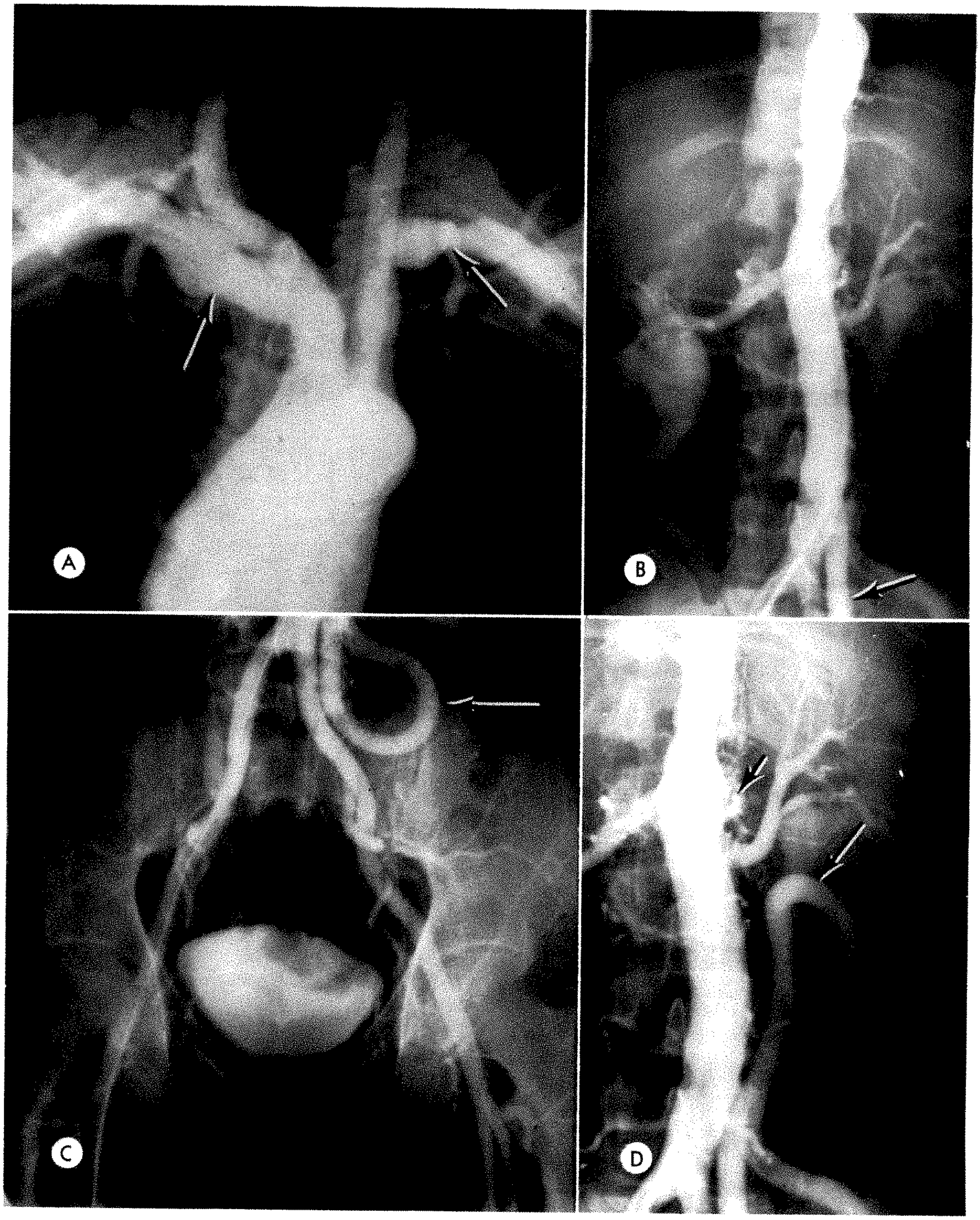


Fig. 1. Case 1. (*A*) There are stenotic areas of both subclavian arteries (arrows). Note the absent left vertebral artery and the enlarged internal mammary arteries. (*B*) There is marked irregularity of the lower thoracic and upper abdominal aorta; however, the renal arteries are normal in caliber. Arrow indicates the dilated inferior mesenteric arterial loop. (*C*) The arterial supply below the dilated inferior mesenteric artery (arrow) is normal. (*D*) The ascending dilated mesenteric artery is located along the left side of the aorta (lower arrow) after it turns from the pelvis. The paravertebral collateral development (upper arrow) probably aids the iliac circulation.

made its turn out of the pelvis, it proceeded upward along the left side of the aorta (Fig. 1*D*) where its course became increasingly more tortuous as it developed into the truly "meandering" mesenteric artery (Fig. 1*E*). After its extremely circuitous course, anastomosis was made with filling of the superior mesenteric artery via its middle colic branch (Fig. 1*F*). The origin of the superior mesenteric artery was obviously occluded at its origin from the aorta, and its lumen was filled distally by the *retrograde* flow from the inferior mesenteric arterial collateral. Further collateral arterial vessels then proceeded from the now filled superior mesenteric artery via the pancreatico-duodenal arcade about the head of the pancreas to fill the gastroduodenal branch of the hepatic artery and thence the celiac axis which was also obstructed at its origin from the aorta (Fig. 1*G*). In this way the vasculature to the abdominal viscera was derived in retrograde fashion from the inferior mesenteric artery to fill the superior mesenteric artery and eventually the celiac axis, both of these latter vessels being obstructed at their aortic origin (Fig. 1*H*).

The patient declined an exploratory laparotomy and was discharged from the hospital on conservative anti-hypertensive therapy. It is believed that the clinical pattern and arteriographic findings are most compatible with an aortitis.

Comment. It became important to inform the patient that the blood supply to his alimentary tract was furnished, in the main, by a single artery, and should he require abdominal surgery or develop symptoms of abdominal vascular disorder, his physicians should be informed of the mesenteric collateral existence. Also, one could argue for the prophylactic creation of additional pathways to the celiac and superior mesenteric arteries.

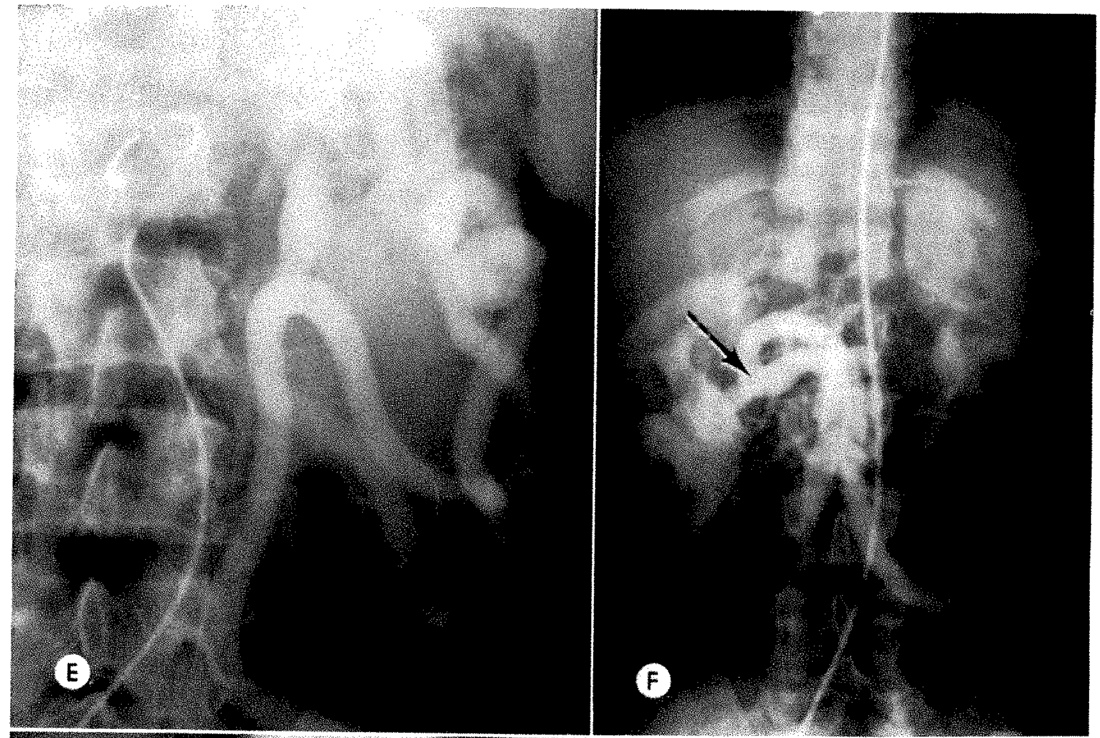
Case II. G.J. is a 14 year old asymptomatic girl discovered to have hypertension on a routine school physical examination. The blood pressure in her right arm was 240/115, and in the left arm was 240/120. The blood pressure in the lower extremities was 160 systolic by palpation. Her pulse was 88 per minute and regular. Other than the hypertension, the most significant physical findings were the presence of vascular bruits. A moderately loud systolic bruit was heard over the abdomen in the midline, in both lower quadrants, and bilaterally over the costovertebral angles. The amplitude of pulsations of the peripheral arteries in the lower extremities was definitely diminished with a significant time lag when compared to the upper extremity and cervical pulsations. Because of the possibility of coarctation aortography was performed.

Findings at Aortography. There was a large vessel arising from the superior mesenteric artery and traveling a moderately tortuous course from the left upper portion of the abdomen to the left lower quadrant (Fig. 2*A*). This vessel then became the inferior mesenteric artery and rejoined the aorta. Collateral vessels were also observed between the celiac axis and superior mesenteric artery (Fig. 2, *A* and *B*).

An exploratory laparotomy was performed. The abdominal aorta was observed to be normal with a gradual taper beginning in the area of the origin of a moderately dilated celiac axis and superior mesenteric artery. Below the superior mesenteric artery the aorta narrowed to a segment measuring approximately 7 millimeters in diameter and several centimeters in length. This narrowed segment involved also the main renal arteries which were markedly diminished in caliber and measured approximately 3 mm. in diameter bilaterally. A strain gauge measurement of the aortic pressures above and below the coarcted segment revealed a 45 mm. Hg differential in pressures between the cephalic and caudal extremes of the narrowed segment of aorta. A large tortuous arterial channel in the left mesocolon coursed through the left upper and lower quadrants of the abdomen and corresponded exactly with the roentgenographic demonstration of this meandering artery. It originated from the superior mesenteric artery, and after running its course, became the inferior mesenteric artery and joined the aorta which was of normal caliber at this level (Fig. 2, *A* and *B*).

Because of the severe renal artery involvement, a corrective vascular repair was not attempted. The patient made an uneventful recovery and was discharged to be followed by the cardiology and vascular surgery services.

Comment. In this case the normal *anterograde* flow of blood is demonstrated as opposed to the retrograde flow of blood demonstrated in Case I. Blood supply to the meandering mesenteric artery is derived, in the main, from the superior mesenteric artery, but collaterals from the celiac axis augment the circulation. Again,



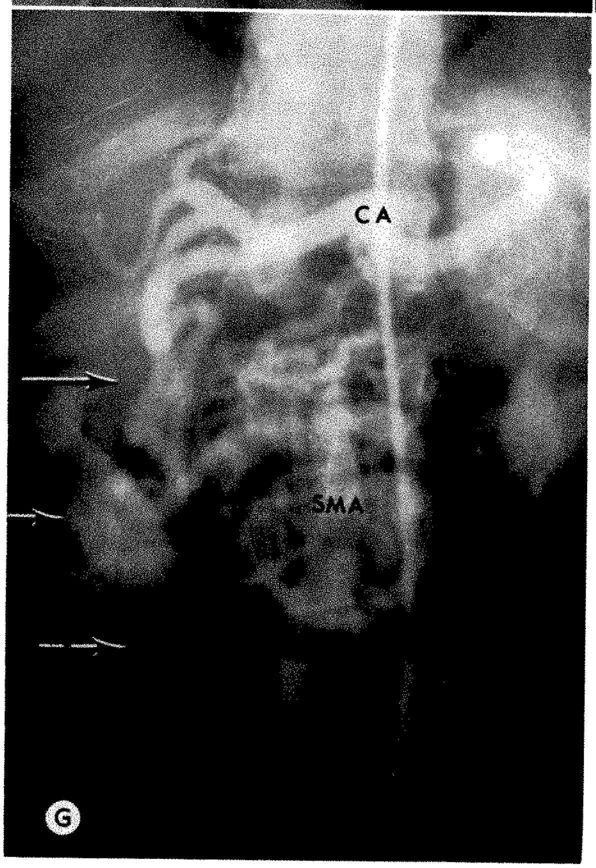


FIG. 1. Case 1. (*E*) An especially circuitous course of the meandering mesenteric artery through the left portion of the abdomen is illustrated. The catheter has been withdrawn to the upper lumbar area of the abdominal aorta. (*F*) Eventual anastomosis of the meandering mesenteric artery with the middle colic branch of the superior mesenteric artery (arrow) is demonstrated. (*G*) The pancreaticoduodenal arcade collateral development (arrows) to fill the celiac axis (CA) from the now filled superior mesenteric artery (SMA) is documented.

the importance to the patient of the demonstration of the altered hemodynamics cannot be overemphasized, and if abdominal surgery is necessary in the future, her surgeons must be aware of this existing circulation.

DISCUSSION

The main impetus to the development of the splanchnic collateral system in the adult is the progression of atherosclerotic disease with age and the resultant vascular compromise. Other causes[4,15] of mesenteric vascular compromise in the adult are embolic phenomena, vasculitis, polycythemia, leukemia, abdominal or pelvic inflammatory disease, neoplastic disease, and cardiac or abdominal surgical procedures. In fact, it has been stated that any patient who develops ulcerative colitis,[2] regional enteritis, or malabsorption syndrome after cardiac surgery or aortic grafting should be suspected of vascular disease until proven otherwise.[15] Naturally, the development of the collateral system of the alimentary tract is favored by the slowest process, as the mortality in acute mesenteric occlusive disease is extremely high.[14]

Mesenteric vascular occlusion in infancy and childhood is rare.[9,13] The mortality

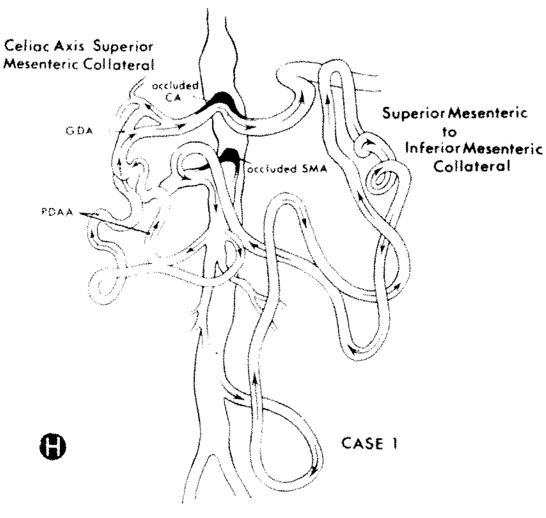


Fig. 1. Case 1. (*H*) A diagrammatic composite of the collateral circulation and the retrograde direction of blood flow in Case 1. Both basic systems are illustrated. GDA = gastroduodenal artery; PDAA = pancreaticoduodenal arcade.

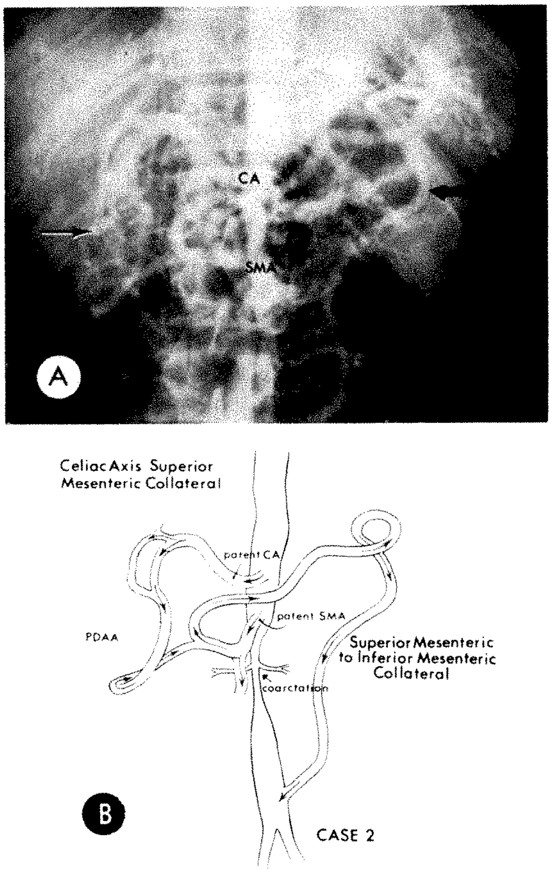


Fig. 2. Case II. (*A*) The meandering mesenteric arterial collateral (large black arrows) provides for increased blood flow from the superior mesenteric artery and celiac axis to the inferior mesenteric artery. Pancreaticoduodenal collaterals (narrow arrow) run between the celiac axis and superior mesenteric arteries. (*B*) Composite drawing of the collateral development in Case II. Note the coarctation of the abdominal aorta and the involved renal arteries which are markedly narrowed in caliber. Small arrows indicate the anterograde flow of blood.

from acute mesenteric vascular occlusion is very high in this age group. The additional causes[13] of mesenteric vascular compromise in younger patients are: emboli associated with congenital heart disease, abdominal trauma, intestinal strangulations, peritoneal bands, coarctation of the aorta, and idiopathic causes.

There are probably three basic reasons for the rare demonstration of the mesenteric collateral system in the younger patient. First, arterial disease is uncommon

in the young patient in contrast to the older adult. Secondly, there is a high mortality when acute mesenteric vascular occlusion occurs in the pediatric age group.[9,13] Thirdly, there is a lower index of suspicion concerning the development of the mesenteric collateral system in the younger patient.

The awareness on the part of the clinician or roentgenologist will be the decisive factor in the demonstration of the splanchnic collateral circulation in the younger patient as the extensive collateral development commonly allows the patient to remain asymptomatic.[3,11,12] The importance to the patient is obvious with respect to contemplated surgery or future abdominal disorders.[2,4,5,11]

The *in vivo* roentgenographic demonstration of the splanchnic collateral potentialities has been illustrated in the presented cases and, relatively recently, has been described in detail by several authors.[1-7,10,12]

SUMMARY

Unusual cases of extensive mesenteric vascular collateral development in 2 young patients are reported. As the extensive collateral development may allow the patient to remain asymptomatic, the clinician or roentgenologist should suspect the development of a mesenteric collateral system when certain vascular abnormalities are encountered in a young patient. These abnormalities include hypertension, diminished upper or lower extremity arterial pulsations, and especially the presence of vascular bruits in the thorax, flank, or abdomen. Recognition and demonstration of this collateral circulation in the young patient will allow for proper surgical intervention if indicated, and will be an invaluable contribution for the evaluation of future medical or surgical disorders in these patients.

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THE VALUE OF ANGIOGRAPHY OF THE SMALL BRANCHES OF THE ABDOMINAL AORTA*

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PROGRESS in selective angiographic techniques has made the catheterization of small branches of the abdominal aorta—*i.e.* the inferior phrenic, adrenal, gonadal and lumbar arteries (Fig. 1) an entirely feasible procedure. It is our purpose in this report to review our experience with over 200 such catheterizations. We will analyze some of the technical factors that lead to a high rate of success, and some anatomic facts that must govern the selection of vessels. In particular, we will stress the diagnostic information that accrues from such studies.

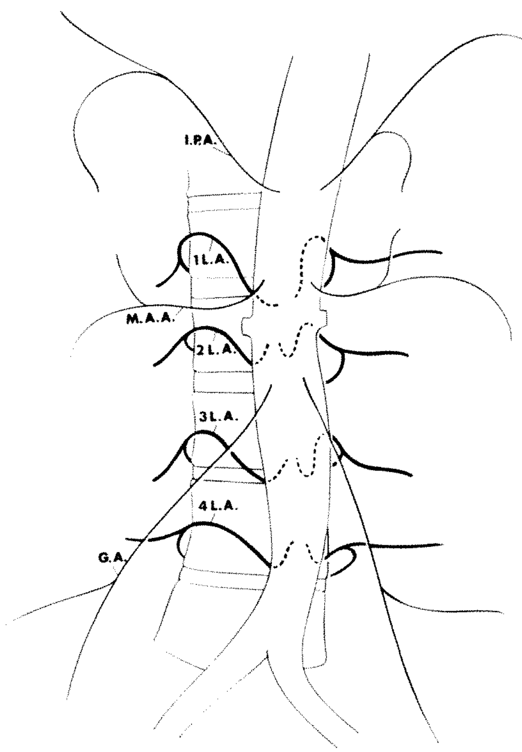

FIG. 1. The small branches of the abdominal aorta, with typical sites of origin. The lumbar arteries (1–4 L.A.) curve around the bodies of their respective vertebrae. The other branches are the inferior phrenic artery (I.P.A.), middle adrenal artery (M.A.A.) and gonadal artery (G.A.)

MATERIAL AND METHODS

The studies included in this review are summarized in Table I. While many of the procedures are performed primarily for the catheterization of the vessels listed, the majority are done in association with other catheterizations, such as renal, celiac and mesenteric. The indications for the studies will be discussed subsequently.

The usual approach is as follows:

1. A high quality aortogram is obtained. This is done by inserting a PE 240 J-tipped catheter 50 cm. in length, and positioning it under fluoroscopy at the level of origin of the vessel of interest. A pressure injection of 30–50 ml. of 60 per cent methylglucamine diatrizoate (renografin 60) or iothalamate (conray) is made at an injection rate of 25–35 ml. per second while serial films are exposed. A Valsalva maneuver is used occasionally in order to decrease flow, or to displace the kidneys. Biplane, stereoscopic and oblique views are sometimes obtained to improve visualization of vessel origins.
2. For selective entry, a BD RPX 054 catheter 50 cm. in length is used. The catheter is tapered to a fine but short point to permit entry into small vessels without buckling of the tip. The end of the catheter is bent into a

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TABLE I
EXPERIENCE WITH CATHETERIZATION OF THE SMALL BRANCHES OF THE ABDOMINAL AORTA

Inferior Phrenic Artery		—Total 90
	Right—30	
	Left—32	
	Common—28	
Gonadal Artery		—Total 15
	Spermatic—11	
	Ovarian—4	
Middle Adrenal Artery		—Total 43
	Right—15	
	Left—28	
Lumbar Artery		—Total 55
	First—21	
	Second—18	
	Third—12	
	Fourth—4	
Total		203

smooth semicircle, with the diameter approximately 30 per cent greater than that of the aorta at the level of origin of the desired vessel. Proximal to this curve the catheter is kept as straight as possible, with no secondary bends for aortic, lumbar or iliac curves.

3. After exchange over an .035 guide wire, the catheter is manipulated into the area in which the desired branch appears to arise. Anatomic knowledge of the usual anterior or posterior relationships of the vessel origin is utilized, as well as the information from the aortogram. The catheter is checked for free back flow of blood, and filled with saline.
4. The catheter is then connected via a flexible tube to a 20 ml. narrow bore syringe filled with contrast agent. While very gentle manipulation of the catheter tip in the area of interest is carried out, injections of 0.2–0.5 ml. of contrast material are made under fluoroscopy. While the catheter is in the aorta, these injections can not be seen since the contrast medium dilutes rapidly with the large blood flow. However, when the small vessels are selectively entered, contrast filling can be observed. No effort to withdraw blood is made during this manipulation except when the syringe is refilled.
5. Whenever the catheter does not readily follow the aortic wall in the region of interest, an exchange is made without undue delay. Either the size of the curve is altered, or in cases of unusual aortic tortuosity a secondary compensating curve is introduced into the replacement catheter. Three or four catheter changes have been used on occasion.
6. With catheter in place in the small artery, a check is made for backflow of blood. If this is obtained, there is little concern about total occlusion of the vessel. About half of the time there is no backflow and a fluoroscopic check is then made to see if the catheter blocks the vessels and delays flow of a test dose of contrast material. If this is the case, the injection is performed nonetheless, but a smaller volume of contrast material is used and the catheter is withdrawn immediately after injection, while the filming is still in progress. The volume of contrast agent varies from 1–15 ml., depending on the size of the vessel. The injection time is 1–4 seconds, and serial films are obtained over an 8–25 second period.

RESULTS

The success rate of small artery catheterization depends firstly on whether the vessel origin can be visualized on the aortogram, secondly, on the experience of the angiographer and thirdly on the condition of the aorta in regard to tortuosity and arteriosclerotic plaques. When the vessels can be identified on the aortogram the success rate in all branches described here exceeds 90 per cent. When the vessel origin can not be seen on aortography, and the position has to be guessed, the success rate varies from 80 per cent in the lumbar arteries to 20 per cent in the gonadal arteries.

The presence of extensive aortic plaques makes the catheterization procedure much more difficult, and is considered a contraindication to study because of a complication encountered early in our experience which will be described below.

The patient usually notes the injections as a feeling of discomfort. Inferior phrenic artery injections are localized to the shoulder, middle adrenal artery injections to the upper flank, and lumbar artery injections to the back. Gonadal artery injections produce less discomfort than the others. The referred sensation is to the lower abdomen.

The only serious complication occurred in a hypertensive 55 year old man who underwent aortorenal arteriography. Aortography showed that extensive arteriosclerosis was present and that the left renal artery was occluded. A selective small vessel catheterization was undertaken in an attempt to demonstrate the blood supply to the left kidney from collateral vessels. The procedure was prolonged because the catheter repeatedly lodged in atheromatous plaques. Several lumbar arteries were entered, however, and injected. A selective arteriogram of the patient's right renal artery following this manipulation showed segmental occlusion of an intrarenal branch which had been patent on the aortogram. Several weeks after the arteriography, the patient developed signs of atheromatous embolization to the legs and progressive renal failure which led to his death about 4 months later. At autopsy, there were atheromatous emboli in the right kidney. This case has been described in detail elsewhere.[4]

Our experience with selective angiography of the adrenal glands has been reported in part.[7,8] We have now demonstrated 11 adrenal tumors by this method. We are impressed by the fact that many tumors, particularly the cortisol secreting adenomas (Fig. 2, *A* and *B*) and adrenal carcinomas appear quite vascular on selec-

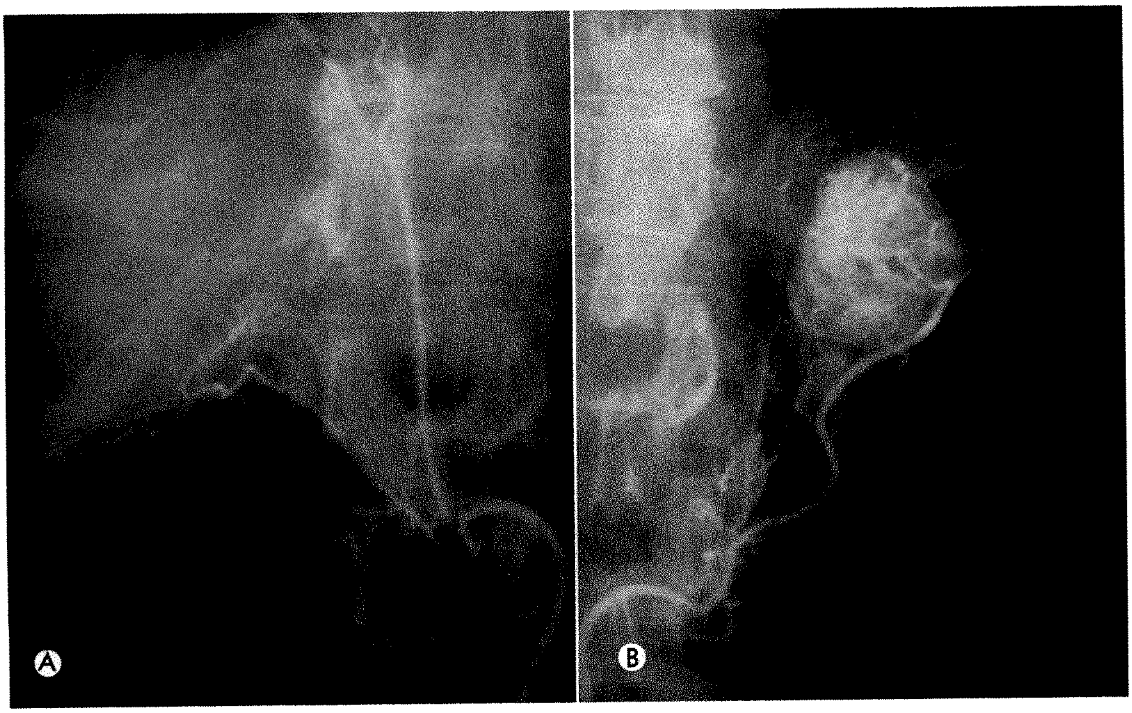

FIG. 2. A 50 year old woman with Cushing's syndrome. (*A*) Selective right inferior phrenic arteriogram. The right adrenal gland is not enlarged. (*B*) Selective left middle adrenal arteriogram. A 3 cm. adenoma is seen in the upper portion of the left adrenal gland.

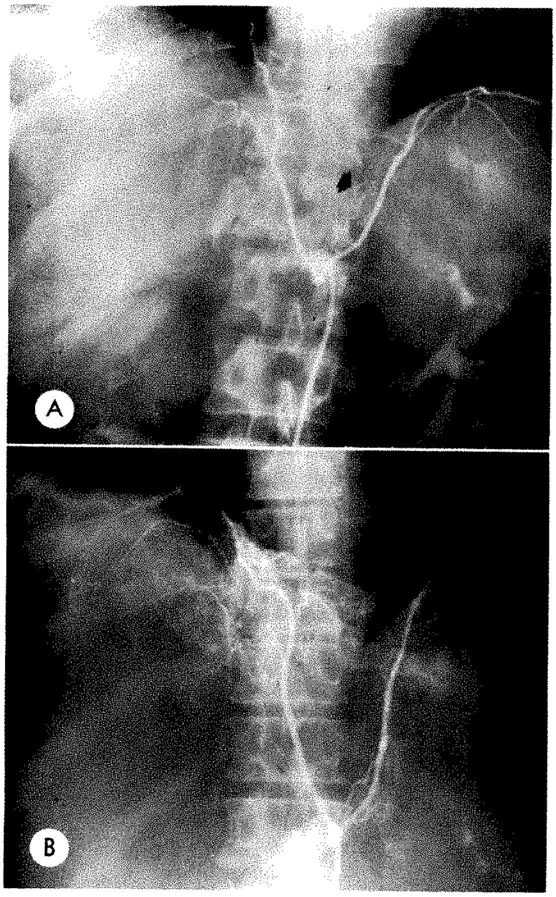

FIG. 3. A 52 year old man with carcinoma of the gastric fundus invading the esophagus. (*A*) Selective common inferior phrenic arteriogram before chemotherapy shows prominent gastric branches to the area of the tumor (arrow). The remainder of the inferior phrenic artery appears normal. (*B*) Repeat selective arteriogram 7 months later. The inferior phrenic arteries have now enlarged considerably, and are supplying both metastasis to the liver and tumor seeding the peritoneum.

tive angiograms, but are not readily detected by aortography. While pheochromocytomas usually are so highly vascularized that they are readily seen on the flush aortogram, in one instance we were able to demonstrate the presence of a tumor only by selective adrenal artery injection. The experience with selective adrenal arteriography in 6 proven aldosteronomas has been disappointing.[10] In one instance it was possible to demonstrate displacement of adrenal arteries by tumor. However, not only are these tumors quite avascular, but significant lesions may be only 1–2 mm. in size. While the pattern seen on adrenal venography has been characteristic in some instances, the use of adrenal venous sampling for aldosterone has been the most valuable localizing test. Adrenal metastases have been demonstrated as negative filling defects in several cases.

Another use of selective adrenal angiography is in the evaluation of gland size in patients with suspected adrenal hyperplasia. While no exact parameters have yet been developed, gross enlargement of both glands on arteriography was apparent in several cases.

Additional observations on the extra-adrenal branches of the inferior phrenic artery confirm our previous observations.[6] In addition to supplying the diaphragm, these arteries also give branches to a major portion of the peritoneum. Collateral branches to the liver on the right, and to the stomach on the left are also prominent. In a number of cases we have seen tumor supply to the liver or stomach arising from the inferior phrenic arteries, and the development of peritoneal seeding in a rapidly advancing gastric carcinoma can be similarly followed (Fig. 3, *A* and *B*). The inferior phrenic arteries are occasionally enlarged as the result of inflammatory or postoperative changes, and the left inferior phrenic artery usually becomes prominent after splenectomy.

Selective perirenal arteriography, or injection of the small branches supplying the area surrounding the kidney has been a useful technique in evaluating the extent of 19 kidney tumors. The presence of tumor vessels filling from these branches indicates spread through the renal capsule. Usually the inferior phrenic artery supplies upper pole tumors, the middle adrenal and gonadal arteries medial lesions, mesenteric branches supply anterior tumors and lumbar arteries posterior and lower pole lesions. The second lumbar artery is the one most often associated with the blood supply of the renal bed.

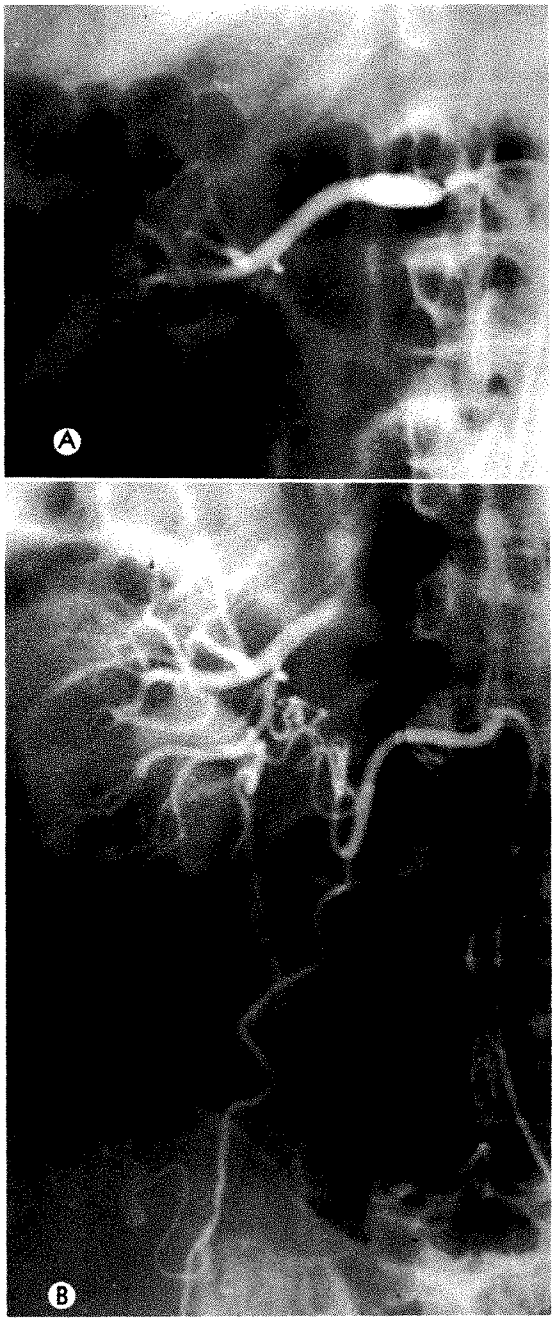

Fig. 4. A 58 year old man with hypertension. (*A*) Right renal arteriogram shows a tight stenosis. (*B*) Selective right spermatic arteriogram demonstrates collaterals furnishing the major blood supply to the right kidney.

The same arteries which furnish blood supply to kidney tumors can also act as collaterals to the renal artery in case of proximal obstruction. Such collaterals are demonstrated in 6 cases in this series, most often from the lumbar arteries, but occasionally from the middle adrenal, inferior phrenic or spermatic arteries (Fig. 4, *A* and *B*). In several instances the distal renal artery cannot be evaluated by aortography, but is seen only after selective injection. All patients in whom collaterals to the kidney are demonstrated were hypertensive. However, in a number of patients with significant renal vascular hypertension no collaterals can be seen on selective injections.

A search for recurrent renal tumors by selective catheterization of the small arteries of the tumor bed was made in 6 cases. In one instance selective lumbar arteriography (Fig. 5, *A*–*C*) demonstrates a recurrence. In another case, recurrent tumor is shown on inferior adrenal and inferior phrenic artery injections. In the postoperative period evaluation of the renal tumor bed is often combined with selective arteriography of other suspected metastatic sites, such as lung, liver and bone.

Other retroperitoneal tumors also frequently receive their main blood supply from the small branches of the abdominal aorta. The middle adrenal artery usually supplies the major retroperitoneal branch, which courses laterally around the kidney in the surrounding fatty tissue. Tumors of the retroperitoneum are therefore frequently best shown on middle adrenal arteriography (Fig. 6), and differentiation has to be made between primary adrenal tumors and lesions of other retroperitoneal tissues. The inferior phrenic and gonadal arteries also contribute significantly to retroperitoneal blood supply. The lumbar arteries supply principally those lesions situated posterior to the dorsolumbar ligament. Extensive lumbar artery supply was seen in a neurilemmoma. The lumbar arteries provide blood to the vertebral bodies, and may be injected to demonstrate lesions in this area (Fig. 7). Blood supply to the spinal cord via the anterior spinal arteries,

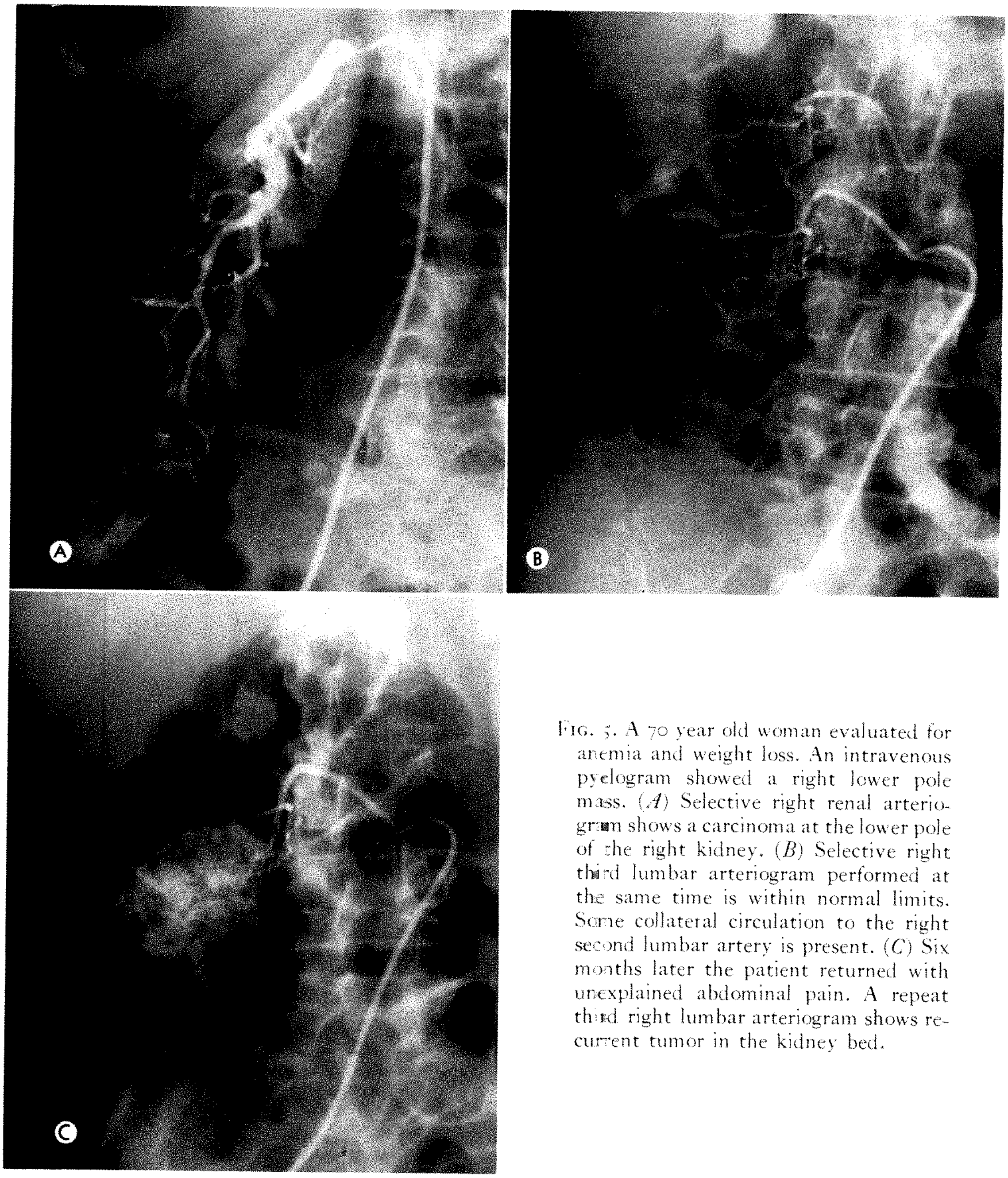

FIG. 5. A 70 year old woman evaluated for anemia and weight loss. An intravenous pyelogram showed a right lower pole mass. (*A*) Selective right renal arteriogram shows a carcinoma at the lower pole of the right kidney. (*B*) Selective right third lumbar arteriogram performed at the same time is within normal limits. Some collateral circulation to the right second lumbar artery is present. (*C*) Six months later the patient returned with unexplained abdominal pain. A repeat third right lumbar arteriogram shows recurrent tumor in the kidney bed.

while most often of intercostal origin, sometimes arises from lumbar arteries. Selective gonadal arteriography was used to demonstrate extension of a uterine sarcoma (Fig. 8). No primary ovarian or testicular tumors have yet been studied, although the excellent demonstration of branches to the testes (Fig. 9, *A* and *B*) makes this possible.

Anatomic observations regarding the direction and level of origin of small abdominal aortic branches are summarized in Table II.

DISCUSSION

Just as the method of selective catheterization of large vessels has become more

reliable with increased use, the technique of small vessel catheterization can also now be undertaken with full expectation of success. The first major application of small vessel catheterization was in the bronchial arteries.[2,13] Selective catheterization of small thoracic branches is in some respects easier and in other aspects more difficult than those of the abdomen. The thoracic aorta is usually straighter and there are fewer confusing branches. However, because of the high blood flow in the thoracic aorta, and the relatively low flow through small arteries, the vessel origins are very difficult to demonstrate on aortography.

The proper design of catheters is the most important single factor in the selective catheterization of small vessels. An aortogram showing the size of the aorta at the level of origin of the side branch is ex-

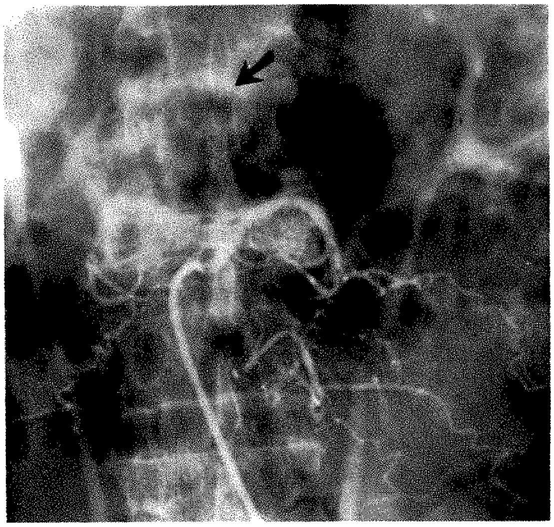

Fig. 7. A 59 year old man with Paget's disease of the second lumbar vertebra detected incidentally during aortofemoral arteriography. Selective left second lumbar arteriogram shows enlargement of the posterior division of the lumbar artery, and some increased vascularity in the diseased vertebral body. An anterior spinal artery is also seen (arrow).

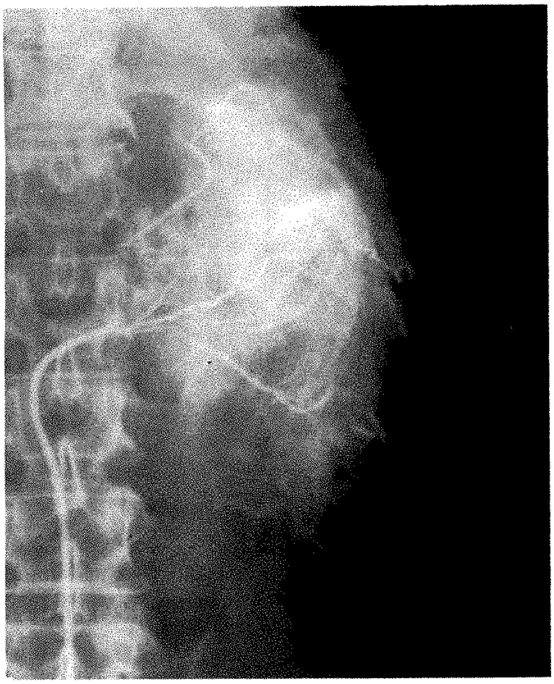

Fig. 6. A 66 year old female with fever of undetermined origin. An intravenous urogram showed lateral and downward displacement of the left kidney. The selective left middle adrenal arteriogram reveals bizarre vessels supplying a large tumor mass which has displaced the left adrenal gland laterally. At surgery this was proven to be lymphosarcoma.

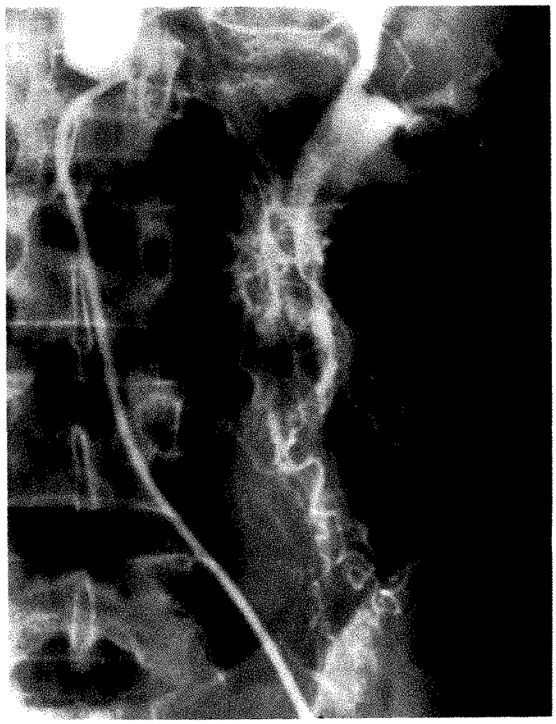

Fig. 8. A 49 year old woman one year post-hysterectomy for uterine sarcoma with recurrent retroperitoneal pain. A selective ovarian arteriogram shows vessels supplying a massive recurrence of tumor.

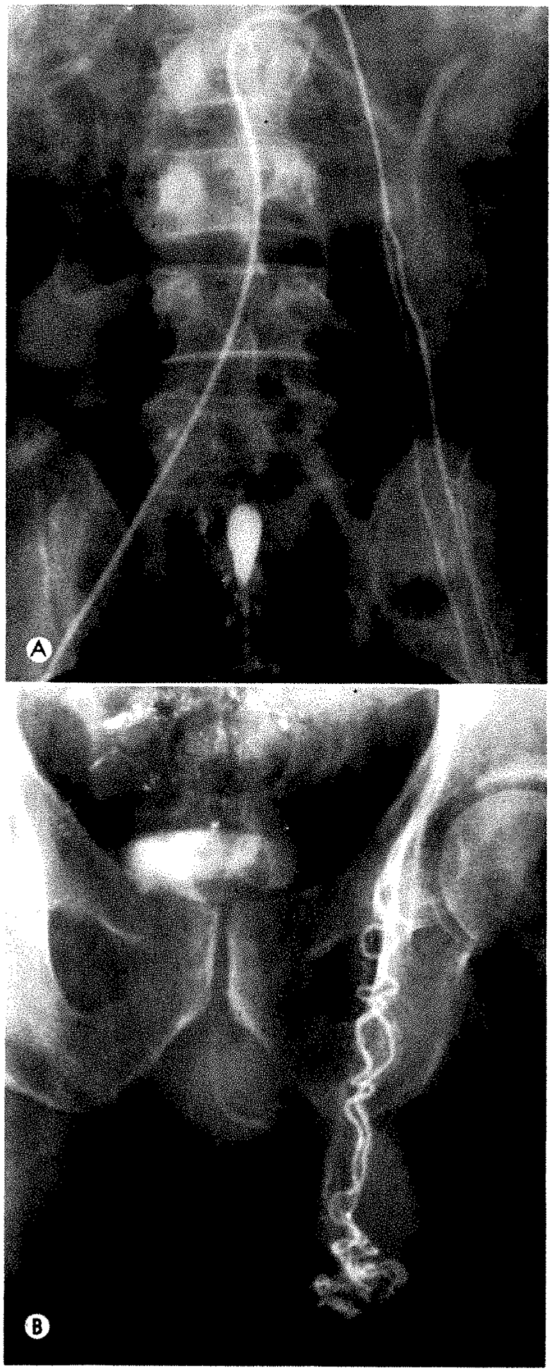

FIG. 9. A 55 year old man being evaluated for possible retroperitoneal neoplasm. Left spermatic arteriogram. (*A*) Upper half. (*B*) Lower half. The findings are normal.

tremely helpful in determining the shape of the catheter. Once the insertion has been made, it is essential to judge whether or not the catheter has just the right amount of contact with the aortic wall in the area of interest, and to replace it promptly if it does not. The insertion of a catheter which has been designed without knowledge of the aortic width in order to save time is self-defeating.

Newer instruments which permit the changing of the tip of the catheter inside the body[1,14,15] will in all probability eventually solve the problem of catheter design. Unfortunately, the instruments currently available have major disadvantages such as stiffness, poor injection characteristics, and tendency to clot formation. Therefore, we continue to use preshaped radiopaque polyethylene catheters.

Not only is careful catheter design essential to success, but it is also one of the principal safety factors in small vessel catheterization. It is well known that the manipulation of selective catheters against the wall of the aorta causes considerable intimal abrasion,[9] and that the severity of the trauma is proportional to the force used. A properly designed catheter will accomplish its purpose more rapidly and with less force, and thus as little damage to the intima as possible.

A problem that has concerned us continually since our one serious complication several years ago, is the possibility of scratching atheromatous plaques, either with immediate embolization, or with the formation of a site for subsequent discharge of atheromatous material or thrombus formation. We believe that this is a potential hazard of all selective catheterizations, not only those involving small vessels, and its incidence is probably related both to the amount of manipulation and amount of disease. Therefore, we consider arteriosclerosis a relative contraindication to selective arteriography. When required, the procedure must be performed with a minimum amount of manipulation.

Table II

DIRECTION AND LEVEL OF ORIGIN OF SMALL ABDOMINAL AORTIC BRANCHES

Artery	Usual Direction of Origin	Usual Level of Origin	Range		Notes
			Upper	Lower	
Inferior phrenic	Anterior or anterolateral	T12–L1 interspace or top 3rd of L1	T11–12 interspace	Top 3rd of L2	May arise from celiac axis or right renal artery
Middle adrenal	Anterolateral or lateral	Middle 3rd of L1	Bottom 3rd of T12	Top 3rd of L2	May arise from inferior phrenic or renal artery
Gonadal	Anterolateral	Top 3rd of L2	Lower 3rd of L1	Middle 3rd of L3	May arise from renal artery (especially on right side)
First lumbar	Posterolateral or posterior	Bottom 3rd of L1	Middle 3rd of L1	Top of L2	Usually larger anterior division and extensive collaterals
Second lumbar	Posterolateral or posterior	L2–L3 interspace	Middle 3rd of L2	Middle 3rd of L3	Posterior division often larger than anterior
Third lumbar	Posterolateral or posterior	Bottom 3rd of L3	Top 3rd of L3	L3–L4 interspace	Anterior divisions directed toward iliac crest
Fourth lumbar	Posterolateral or posterior	Middle L4	Top 3rd of L4	Aortic bifurcation	May arise from iliac artery or midsacral artery

Another potentially hazardous step in small vessel catheterization is the need for the injection of contrast material without prior aspiration of blood. This is essential, because when the small branches are entered successfully, it is frequently not possible to aspirate blood. Two precautions are necessary. First, the syringe containing contrast material must already be attached to the catheter, so that a bubble of air will not inadvertently be injected. Secondly, the injection must be made gently with a small amount of contrast medium. When the catheter is lodged against the aortic wall, resistance will usually be encountered and no injection made. Occasionally a small subintimal deposition of contrast material occurs. This has caused no clinical sequelae in our experience.

Another potential hazard is created by the total occlusion of a small aortic branch by the catheter. We believe that the collateral blood supply to all these arteries through the many interconnections that constitute the plexus of Turner is adequate so that a few minutes of occlusion will not produce tissue damage. The greater risk occurs during and after the injection of contrast medium. It is easy to overinject the small vessels, and the contact of the contrast medium with the endothelium may be unduly prolonged. The principal risk to the patient probably occurs if the main anterior spinal artery (artery of

Adamkiewicz) arises from a lumbar artery injected in this manner. There is no doubt that the relative safety of the 60 per cent methylglucamine salt of the modern contrast media reduces the risk of spinal damage. We believe it is essential to minimize the volume injected into an artery occluded by the catheter, and to withdraw the catheter immediately after conclusion of the injection. It is often distressing to have to withdraw a catheter from an artery for which one has searched a long time, without knowing whether additional injections in that artery might subsequently be desirable. However, even if the patient suffers no permanent tissue damage, the discomfort he will experience with a blocked artery filled with contrast material will be quite considerable. Furthermore, once the exact location of an artery is known, re-entering the vessel will usually not prove difficult.

Once the technique of small vessel catheterization has been mastered its uses become surprisingly numerous. Frequently it will be applied in conjunction with selective catheterization of major arteries. Thus, perirenal arteriography is valuable in determining the extent of kidney tumors. Similarly, in evaluating patients with tumors of the stomach, pancreas and liver for intra-arterial chemotherapy, selective catheterization of small branches frequently provides additional information about neoplastic blood supply. In the study of the patient with renal vascular hypertension, selective injection of the small branches is sometimes the only way to show the peripheral segment of a proximally occluded renal artery. In other instances the demonstration of collateral vessels provides substantiating evidence that a stenotic lesion is significant.

In an increasing number of cases we are undertaking selective arteriography of small vessels as a primary procedure. This is particularly true in adrenal angiography, which is performed both for the demonstration of tumors and the evaluation of adrenal size. While some adrenal branches may be seen on the renal arteriogram after epinephrine,[5] the optimum adrenal visualization is produced by selective injections of the middle adrenal and inferior phrenic arteries.

Selective catheterization of the small branches of the abdominal aorta is also a key to demonstrating other lesions of the retroperitoneum. Selective arteriography of the gonadal arteries has not yet found much application. In the male, the simplicity of physical examination of the testes and relatively minor surgery required for exploration may limit the role of arteriography. However, it is possible that arteriography of the ovaries may prove a valuable diagnostic procedure.

In recent years some interest has developed in selective arteriography of vascular malformations of the spinal cord.[3] Selective arteriography of the lumbar arteries also furnishes an opportunity for study of lesions of both the vertebral bodies and soft tissues of the back.

It is necessary to be cautious in interpreting angiograms of the small branches of the abdominal aorta. Congenital variations in the distribution of these blood vessels are extensive. Muscular blushes resulting from the overinjection of small vessels can easily be mistaken for tumor, as can the collateral networks which result from previous surgery or arteriosclerosis. The adrenal glands are subject to great variations in shape, and these must also be interpreted carefully. Fortunately the abnormalities seen on selective catheterization of the small abdominal aortic branches frequently are quite gross.

SUMMARY

We have reviewed our experience with over 200 selective catheterizations of small branches of the abdominal aorta.

The technique requires preliminary aortography, accurate catheter design, and careful manipulation with repeated small volume contrast material injections.

The method has proven highly useful in evaluating the extent of renal and other abdominal tumors, in demonstrating the

renal artery distal to an occlusion, in evaluating adrenal size and masses and in studying other lesions of the retroperitoneum. It shows promise in the evaluation of lesions of the gonads, spinal cord, vertebral bodies and other structures of the back.

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ANGIOGRAPHIC DEMONSTRATION OF CROSS PELVIC COLLATERAL CIRCULATION FOLLOWING BILATERAL AXILLARY FEMORAL BYPASS*

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THE presence of a rich, well developed cross pelvic collateral circulation in patients with obstructive disease in the iliofemoral arterial system has been well demonstrated angiographically by numerous authors.[2–6,8,11] The vascular radiologist has assumed an important role in the diagnostic evaluation and postsurgical management of patients with vascular disease particularly following the use of replacement or bypass grafts. Axillary femoral bypass as first successfully accomplished by Blaisdell and Hall[1] is a rather new approach to the treatment of an infected aortic graft. Therefore, reports demonstrating the hemodynamics of such bypass grafts have been rather sparse. It is the purpose of the authors to illustrate the presence of a cross pelvic collateral circulation when one side of the graft is voluntarily occluded proximal to the point of pelvic inflow in a patient with an infected aortico-iliac graft.

REPORT OF A CASE

W.B., a 52 year old white male, was admitted January 4, 1966, complaining of low back pain which radiated down the right leg, and was due to traumatic degenerative disk disease. A myelogram showed a small protrusion in the interspace of L5-S1. There was no associated neurologic deficit. An incidental abdominal aortic aneurysm was palpated at the time of his admission. A 6.5 × 7 cm. abdominal aortic aneurysm was removed at operation and was replaced with an aortico-iliac knitted dacron prosthesis. The patient was discharged on the ninth postoperative day with all wounds healed.

Five weeks later he was re-admitted for malaise and coccydynia and discharged without treatment.

He was re-admitted for a third time 2½ months after the original procedure with chills and fever unresponsive to antibiotics. The chills and fever finally subsided and his only symptoms were low back pain, tenderness over the left flank and limitation of straight leg raising to 45°. Intravenous pyelography revealed a nonfunctioning left kidney and retrograde pyelography showed a severely stenotic left ureter with proximal hydronephrosis.

Upon failure to dilate the stenotic area, exploratory laparotomy was carried out which revealed a kidney surrounded by pus, connected to a large cortico-nephric abscess. Reactive fibrosis had surrounded the ureter producing the stenotic area. Distal to this fibrotic area, a "loculated retroperitoneal hematoma" was found. Clots were removed from "the hematoma," the left ureter reconstructed and the wound closed and drained. The aortic prosthesis was never visualized during this procedure.

Five days after this operation, the patient bled profusely from the left aortico-iliac anastomosis and associated false aneurysm. The separated ends of the anastomosis were resutured for expediency since the patient was in no condition to withstand further operative intervention. At the same time a long stasis clot was removed from the iliofemoral arterial system by means of a Fogarty catheter.

Three weeks later the left iliac suture line ruptured again producing abdominal pain, left flank swelling and shock. At this time a bilateral axillary femoral dacron bypass prosthesis was inserted, the aortico-iliac prosthesis resected, and the left kidney and ureter removed (Fig. 1; Table 1). Postoperatively the patient recovered rapidly and was discharged

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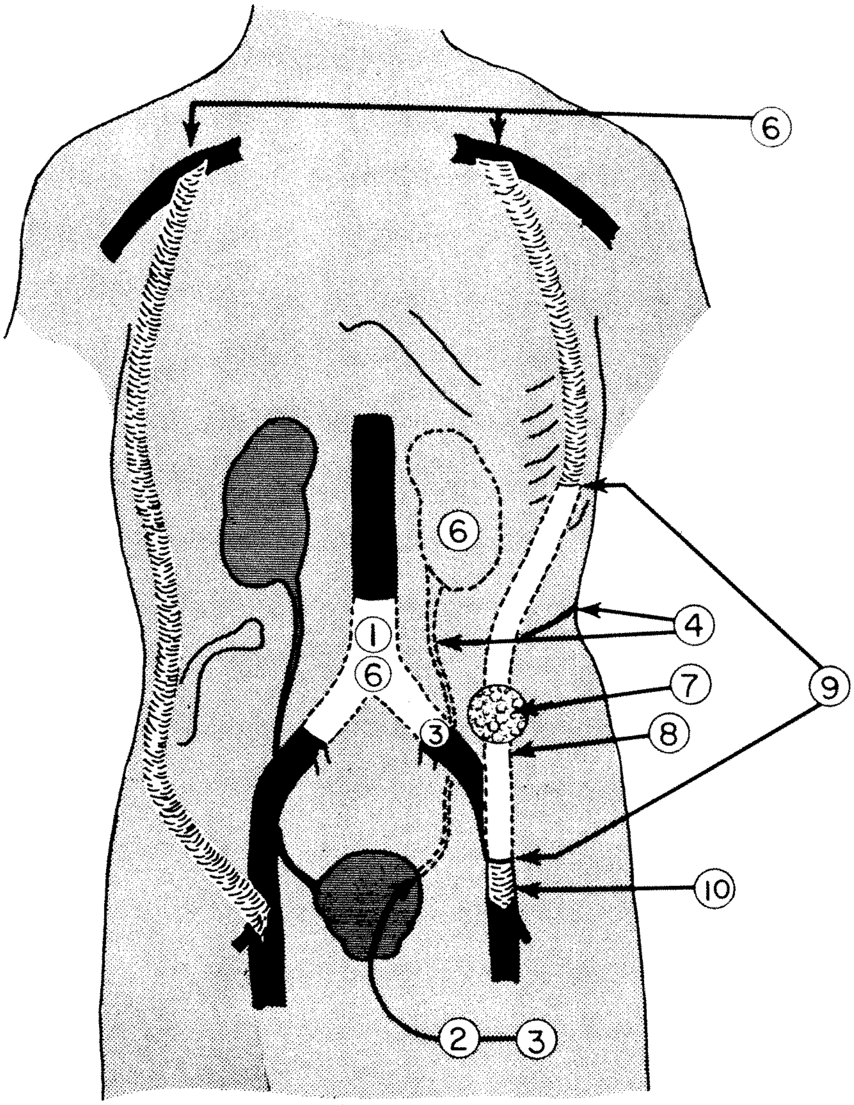

Fig. 1. Diagram of operative procedures: (1) Aneurysmectomy and placement of an aortico-iliac knitted dacron prosthesis; (2 and 3) retrograde cystoscopy and dilatation of the left ureter; (4) drainage of a left cortico-perinephric abscess and reconstruction of the stenotic left ureter; (6) removal of the septic aortico-iliac prosthesis, left kidney and ureter and placement of bilateral axillary artery femoral bypass prosthesis; (7) wide excision of the infected sinus tract around the lower left bypass graft; (8 and 9) partial excision of the left bypass graft; and (10) removal of the remaining distal prosthesis and insertion of a patch graft to the femoral artery defect.

3 weeks after the aortico-femoral bypass procedure.

During July and August 1966 the patient was re-admitted to his local hospital because of upper gastrointestinal bleeding secondary to a hiatus hernia, esophagitis and esophageal peptic ulcer. He recovered from this episode on conservative treatment. In August, 6 weeks after his axillary femoral graft, he developed an infected sinus in the left inguinal area which communicated with the left bypass graft 4 cm. proximal to, but not connected with, the distal anastomosis.

On September 18, 1966, three months after removal of the aortico-iliac prosthesis he was re-admitted for the fourth time to hospital because a large area of cellulitis had developed around the sinus tract. Drainage from

TABLE I

SUMMARY OF COMPLICATIONS AND THEIR OPERATIVE TREATMENT

Admission	Date	Diagnosis	Operation
1	Jan. 4, 1966	Lumbar disk disease	
	Jan. 19, 1966	Abdominal aortic aneurysm	Aneurysmectomy; aortico-iliac dacron graft
2	Mar. 3, 1966	Malaise, coccydynia	None
3	Apr. 4, 1966	Fever, malaise	
	Apr. 6, 1966	Stenotic left ureter, hydronephrosis	Cystoscopy; ureteral drainage
	Apr. 13, 1966	Stenotic left ureter, hydronephrosis	Cystoscopy; ureteral drainage
	Apr. 20, 1966	Cortico-perinephric abscess of kidney	Drainage abscesses; reconstruction of left ureter
	Apr. 25, 1966	Hemorrhage and shock	Resuture of left iliac anastomosis
	May 16, 1966	Hemorrhage and shock	Bilateral axillary femoral bypass graft; resection of aortico-iliac graft, left kidney and ureter
4	Sept. 18, 1966	Infected left axillary femoral graft	
5	Jan. 30, 1967	Infected left axillary femoral graft	
	Feb. 2, 1967		Right percutaneous transaxillary arteriography
	Feb. 8, 1967		Cross clamp of left axillary femoral bypass graft—24 hours
	Feb. 9, 1967		Removal of infected portion of left axillary femoral graft
	Mar. 15, 1967	Infected left femoral cuff	Removal of femoral prosthetic cuff; venous patch graft of femoral artery defect

the wound was cultured and the patient placed upon the appropriate antibiotic therapy. Two days later the sinus and the inflamed tissue were widely excised down to the graft. The wound was packed open and irrigated with the appropriate antibiotic solution. Two and one half months of treatment failed to heal the wound. During this period oral oxicillin was given to discourage the formation of septic emboli.

On January 30, 1967, one year after the initial aortico-iliac graft, the patient was readmitted to hospital with an abscess and cellulitis just proximal to the sinus. The abscess was drained and the inflammation subsided. After occluding the left bypass a right transaxillary arteriogram showed collateral circulation from the right leg to the left leg via the right iliofemoral system (Fig. 2; and 3, *A-C*). In an attempt to determine the viability of the left leg the left prosthesis was carefully clamped. Fifty milligrams of heparin was instilled into the proximal portion of the prosthesis to prevent clotting. There was no evidence of ischemic change in the left foot during the next 24 hours, and that portion of the graft involved in infection was then removed. This left behind the proximal half and distal 1 cm. of the graft.

The left leg and foot remained free of ischemic change.

The upper wound healed without incident, but the cuff of prosthesis left at the femoral anastomosis site became infected and did not heal. This cuff was removed and the defect in the common femoral artery was closed with a brachial venous patch graft. (The saphenous systems were left intact in case a bypass graft would have to be performed at a later date.) The wound was allowed to granulate in the presence of a constant irrigation of antibiotic fluid and it healed without incident.

The patient was discharged from hospital 1 year and 3 months after the initial operation with all wounds healed. The leg and foot have remained viable and the patient can now walk up to one half mile without claudication. (He has not tried to walk further as yet.) At his last visit, a dorsalis pedis pulse was demonstrated, his foot was warm and there were no trophic changes present.

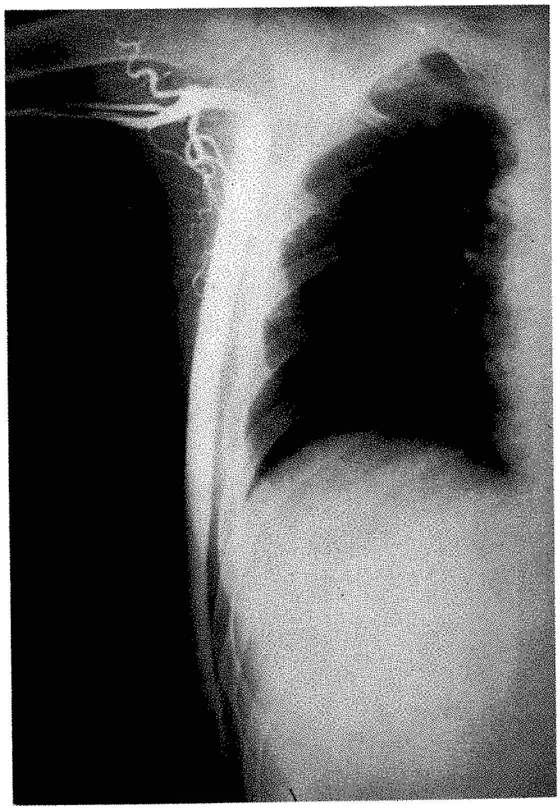

Fig. 2. Angiogram of axillary bypass graft. A catheter has been inserted into the proximal graft site via right brachial artery. There is a dilution defect due to nonopaque blood reaching the anastomotic site from the right subclavian artery. The graft is well opacified in the subcutaneous tissues of the lateral thoracic wall. Note moderate hypertrophy of some of the muscular branches of the axillary artery distal to the anastomosis.

DISCUSSION

Collateral circulation to the pelvis and lower extremities is of vital importance when there is gradual obstruction of the aorto-iliac system. Such a circulation may follow a variety of pathways but, in general, the level of occlusion will determine greatly the type of collateral circulation and, usually, the potential anastomotic channels nearest the site of occlusion are those which partake most actively in supplying blood about the obstructed area. The usual patterns of pelvic and lower extremity collateral circulation have been well described in the past and will not be repeated in detail here. Basically, however, one may expect the collaterals to be either systemic-systemic or viscero-systemic in type. In the former, the intercostal, lumbar, internal mammary, deep circumflex iliac and inferior epigastric arteries all supply blood to the internal and external iliac system, while in the latter the celiac, superior and/or inferior mesenteric arteries may anastomose with the internal iliac arteries through the hemorrhoidal plexuses.

The two basic collateral systems may be equally well developed or one may dominate. The level of aortic occlusion, the severity of the stenotic process, and degree of patency of the mesenteric and internal iliac vessels, all are factors determining whether the systems are balanced or not.

It is also well known that the various branches of the hypogastric artery, both visceral and parietal, are capable of anastomoses with their opposing fellows across the midline as is frequently observed when unilateral pelvic artery obstruction occurs.

The surgical management of patients in which an aortico-iliac prosthesis has become septic will be described in a separate publication.[9] The primary purpose of this report is to point out that a unilateral axil-

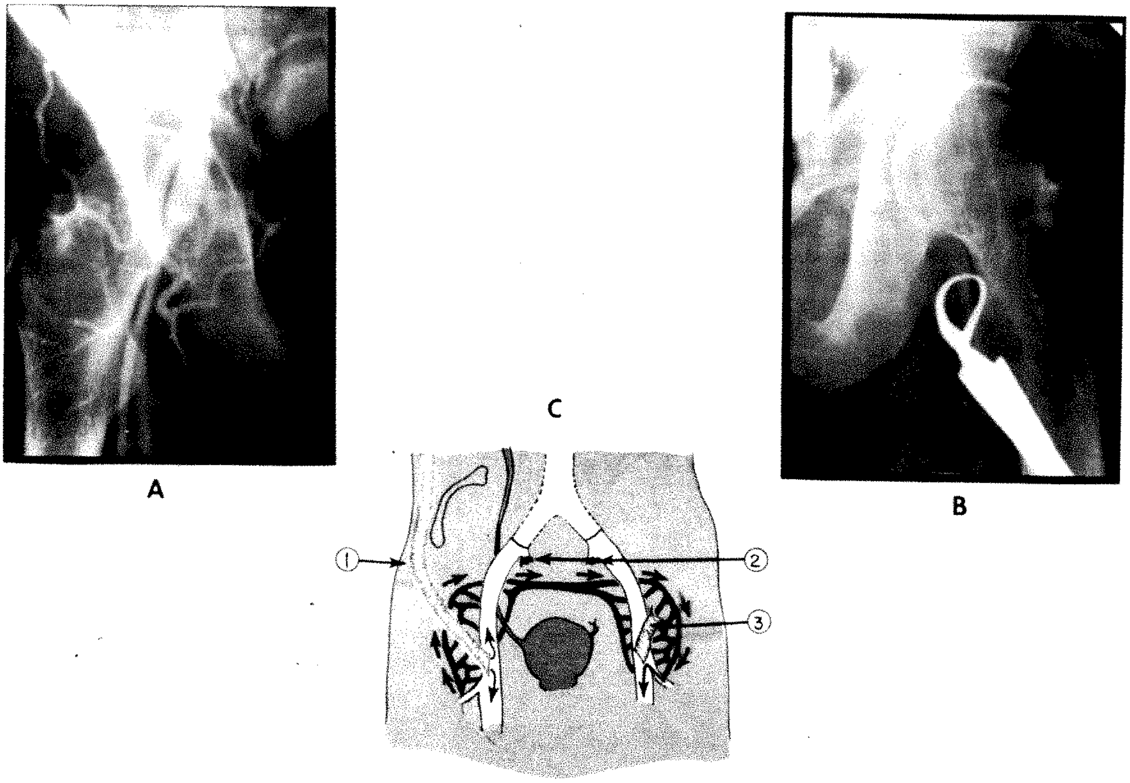

FIG. 3. Right percutaneous transaxillary arteriogram with left bypass graft occluded. (*A*) Angiogram of distal anastomotic site. There is slight narrowing of the graft at junction with the superficial femoral artery and retrograde flow to the bifurcation of the common femoral artery with filling of a hypertrophied deep femoral artery which provides a collateral supply to the right hypogastric system, particularly via the femoral circumflex artery. Both the superficial femoral and deep femoral vessels may be identified more distally. (*B*) Angiogram of left hip and leg at 9 seconds after injection following occlusion of left bypass graft demonstrating the contrast medium faintly outlining the left femoral system (through jaw of towel clip), confirming the presence of a cross pelvic vascular supply to the left leg via the right hypogastric system. (*C*) Diagram demonstrating route of the circulation from the right axillary femoral bypass to the profunda-gluteal-iliac system into the left femoral system: (1) Right axillary femoral bypass; (2) right and left internal iliac origins; (3) cuff of left bypass graft remaining after operation No. 9.

lary femoral bypass graft may be sufficient to nourish both lower extremities by making use of the pre-existing cross pelvic collateral vascular network.

In this particular case, it was noted at surgery following temporary occlusion of the left bypass graft that vigorous backbleeding occurred from the left profunda femoris artery, while there was little flow observed from the common femoral artery indicating that the primary supply to the superficial femoral artery and lower limb on the left was via the femoral circumflex-profunda network. This supply must have originated from the right profunda-gluteal and hypogastric systems and crossed the pelvis to the left hypogastric and profunda-gluteal vessels which nourished the lower limb. A similar but not identical bilateral supply to the lower extremities via a unilateral trans-rectus sheath arterial bypass has been demonstrated by Wolf and Pate.[10]

During the radiologic and angiographic evaluation of the patient who has recently undergone prosthetic replacement of a diseased aorta, the following principles concerning septic retroperitoneal grafts should be kept in mind.[7]

1. Sepsis involving retroperitoneal grafts commonly becomes apparent months after grafting, with ureteral strictures as an accompaniment, and ultimately leads to major hemorrhage from the suture lines.
2. A primary surgical effort directed at the genitourinary region may compound the problem.
3. Ureteral strictures secondary to an infected graft will disappear if the foreign body is removed and the sepsis cleared.

In retrospect, a successful conclusion to this case could probably have been obtained more rapidly had the previous principles been more closely adhered to from the time at which the complications of perinephric abscess and ureteral stricture began to produce symptoms of urinary tract disease.

SUMMARY

A case is reported in which bilateral axillary femoral bypass grafts were performed for aortico-iliac sepsis in a 52 year old white male.

Collateral circulation via the right bypass graft which was adequate to maintain viability of the left leg when the left bypass was clamped is demonstrated and discussed.

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PELVIC ARTERIOVENOUS MALFORMATIONS*

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INTRA-ABDOMINAL arteriovenous communications following trauma or surgery are well documented in the medical literature.[1,3,7,8] In these cases, the history is helpful in establishing the correct diagnosis. In the congenital variety of arteriovenous malformation, however, the diagnosis may be obscure. Recently, we have encountered 2 cases of congenital arteriovenous malformations in relatively young men that presented as mass lesions in the pelvis. Appropriate angiographic study was decisive in establishing the diagnosis and directing the mode of treatment.

REPORT OF CASES

CASE I. A 27 year old white physician was admitted to The Mount Sinai Hospital with the chief complaints of burning on urination and dull suprapubic pain. These complaints had been intermittent for many years. He also experienced occasional pain in the left thigh and testicle on walking. No blood was noted in the semen. After each of two episodes of hematuria, cystoscopy was performed. On both occasions, an extrinsic pressure deformity was noted on the left side of the bladder. There had been no pelvic surgery or prior trauma.

The general physical examination was normal. Blood pressure was 120/70. No abnormality of the external genitalia was noted. The positive findings were limited to the rectal examination which disclosed the presence of a mass related to the left side of the prostate and bladder and extending laterally. It was thought that this represented a cystic, dilated seminal vesicle. One examiner, however, thought the mass was pulsatile and felt a thrill. Examination of the urine showed no abnormalities.

Intravenous urography revealed an extrinsic pressure defect on the left side of the bladder and medial deviation of the distal left ureter (Fig. 1). Because of the pulsatile nature of the mass, the possibility of a vascular neoplasm or aneurysm of the iliac artery was considered and

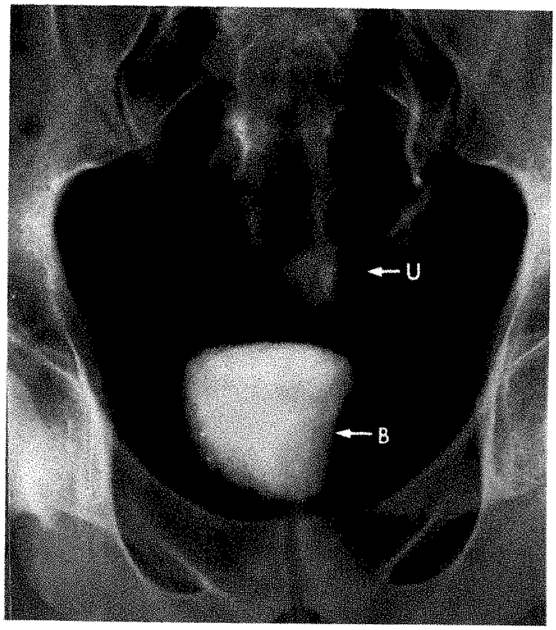

FIG. 1. Case I. Intravenous pyelogram, frontal projection. There is a soft tissue mass displacing the distal left ureter (U) medially and causing extrinsic pressure on the left lateral bladder wall (B).

aortography was performed. A catheter was inserted percutaneously into the right femoral artery by the Seldinger technique and advanced into the lower lumbar aorta. Thirty cubic centimeters of renografin 76 was injected with pressure syringe and serial roentgenograms of the pelvic vasculature obtained. The left hypogastric artery was enlarged. Its branches within the pelvis communicated with a network of tortuous and disorganized vascular channels which drained into large saccular veins which in turn emptied into the inferior vena cava (Fig. 2, *A* and *B*). The findings were consistent with a diagnosis of arteriovenous malformation.

Surgery revealed that the left seminal vesicle was virtually replaced by a vascular mass which proved to be an arteriovenous malformation. This was successfully resected. The patient has returned to work.

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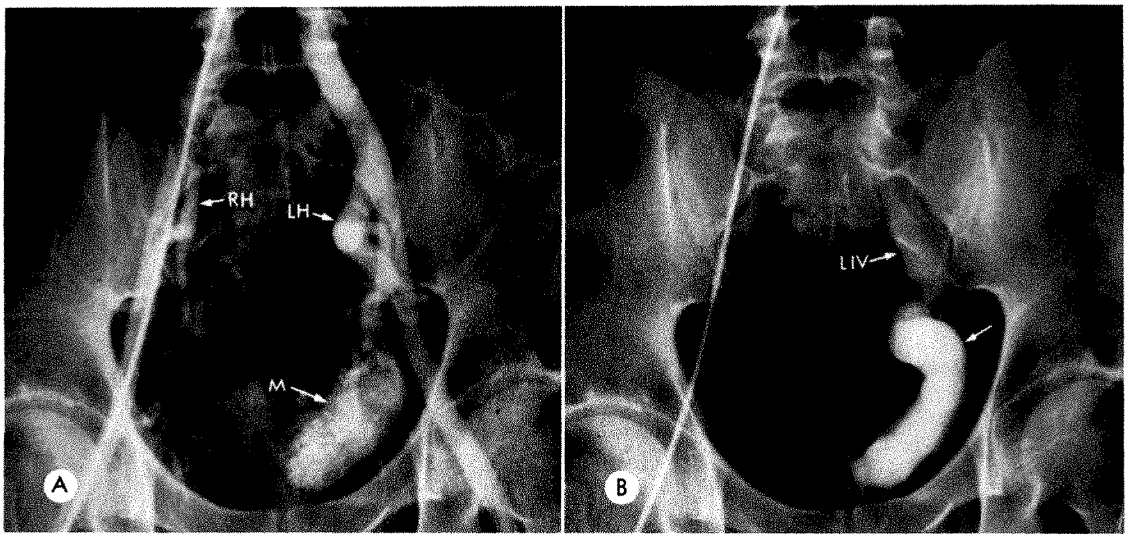


Fig. 2. Case I. Aortograms via right femoral artery. Frontal projection. (*A*) An early aortogram shows a mass of dilated tortuous vessels representing an arteriovenous malformation (M). This is fed mainly by branches of the left hypogastric artery (LH) which is much larger than the right hypogastric artery (RH). (*B*) A later aortogram reveals dilated veins (arrow) draining the vascular malformation into the left iliac vein (LIV).

Case II. A 39 year old white male was admitted to The Mount Sinai Hospital with the chief complaints of dysuria and frequency of urination. There was also a history of impotence of 2 months' duration. There was no history of hematuria. The patient had never undergone pelvic or abdominal surgery.

The general physical examination was normal. Rectal examination revealed a soft tubular mass in relation to the right posterior aspect of the bladder. Urine examination was normal.

Intravenous urography revealed the presence of a mass displacing the right side of the bladder and the distal ureter medially (Fig. 3). Barium enema examination showed that the mass indented the rectum and displaced it to the left (Fig. 4).

The patient was cystoscoped and extrinsic pressure on the right bladder wall was noted. The mucosa of the bladder appeared normal except for one small area of granular tissue on the right lateral wall. A biopsy was attempted. This was followed by severe bleeding which required repeated fulguration for hemostasis.

The initial clinical impression was that the patient had subacute seminal vesiculitis. He was discharged on antibiotic therapy. Bleeding recurred, however, and the patient was readmitted for transfusion and further work-up.

Physical examination on the second admission revealed that the pelvic mass was pulsatile. No bruit was heard.

Percutaneous retrograde aortography and right selective iliac arteriography were performed. The right hypogastric artery was

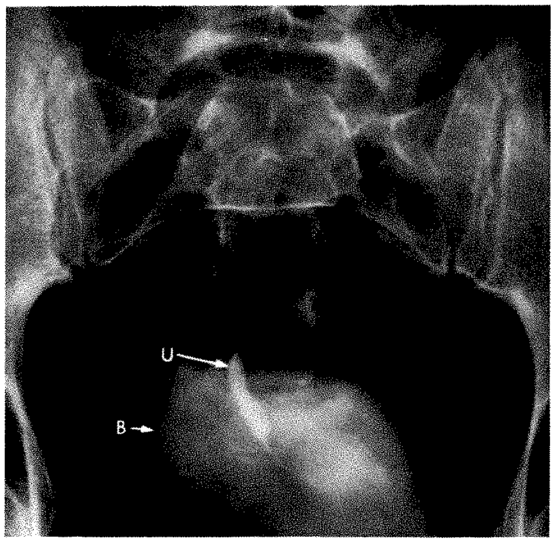


Fig. 3. Case II. Intravenous pyelogram, frontal projection. The distal right ureter (U) is deviated medially and there is extrinsic pressure on the right lateral bladder wall (B) suggesting the presence of a soft tissue mass on the right side of the pelvis.

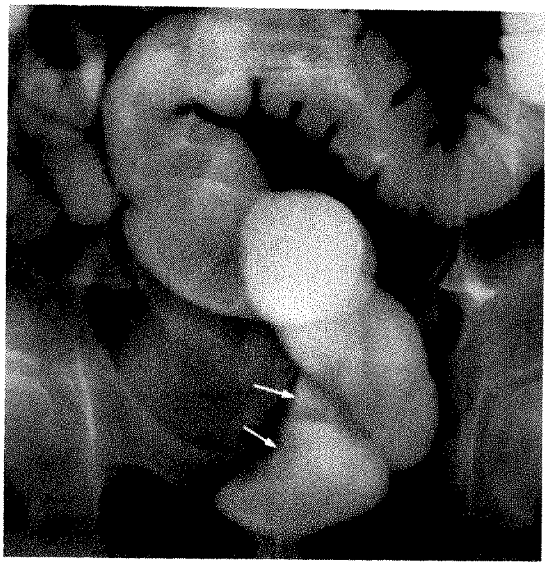


FIG. 4. Case II. Barium enema examination, frontal projection. There is extrinsic pressure on the right lateral rectal wall (arrows) by a soft tissue mass.

markedly enlarged. Its branches in the pelvis were dilated and communicated with an extensive network of abnormal vessels which filled the right side of the pelvis and seemed to involve the base of the bladder and the area of the prostate (Fig. 5*A*). These vessels communicated with a series of large dilated saccular venous channels that emptied into the inferior vena cava (Fig. 5*B*). There appeared to be some flow from the branches of the left hypogastric artery into this vascular malformation.

Surgery was performed and the right hypogastric artery was ligated. The major arteriovenous communication was identified and excised. At this point the venous pulsations ceased. At the time of surgery, it was noted that many dilated vessels also involved the wall of the bladder and rectum. The vesical bleeding stopped after surgery but recurred again in 4 days. Repeat aortography and left common iliac arteriography were performed. These studies revealed prompt filling of the

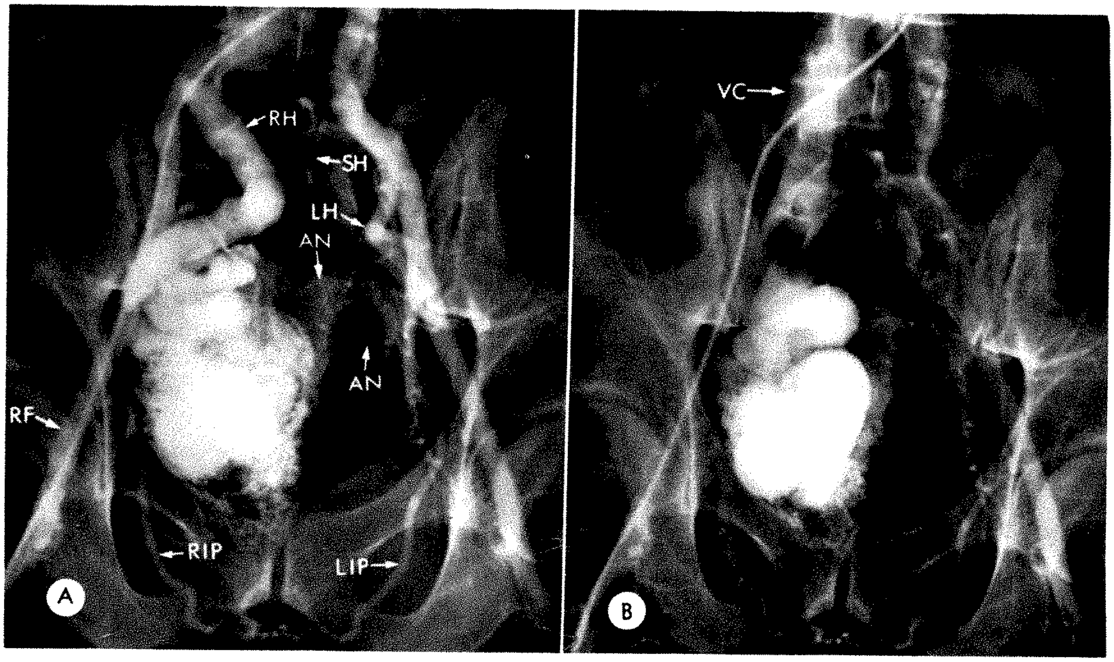


FIG. 5. Case II. Aortograms via right femoral artery. (*A*) An early aortogram reveals filling of a mass of dilated tortuous vessels representing an arteriovenous malformation (M) which is fed primarily by branches of the right hypogastric artery (RH) which is markedly dilated. Several small anastomotic branches (AN) from the left hypogastric artery (LH) appear to enter the vascular malformation. (RF) right femoral artery; (SH) superior hemorrhoidal artery; (RIP) right internal pudendal artery; (LIP) left internal pudendal artery. (*B*) A later aortogram shows dilated venous channels draining the malformation into the inferior vena cava (VC).

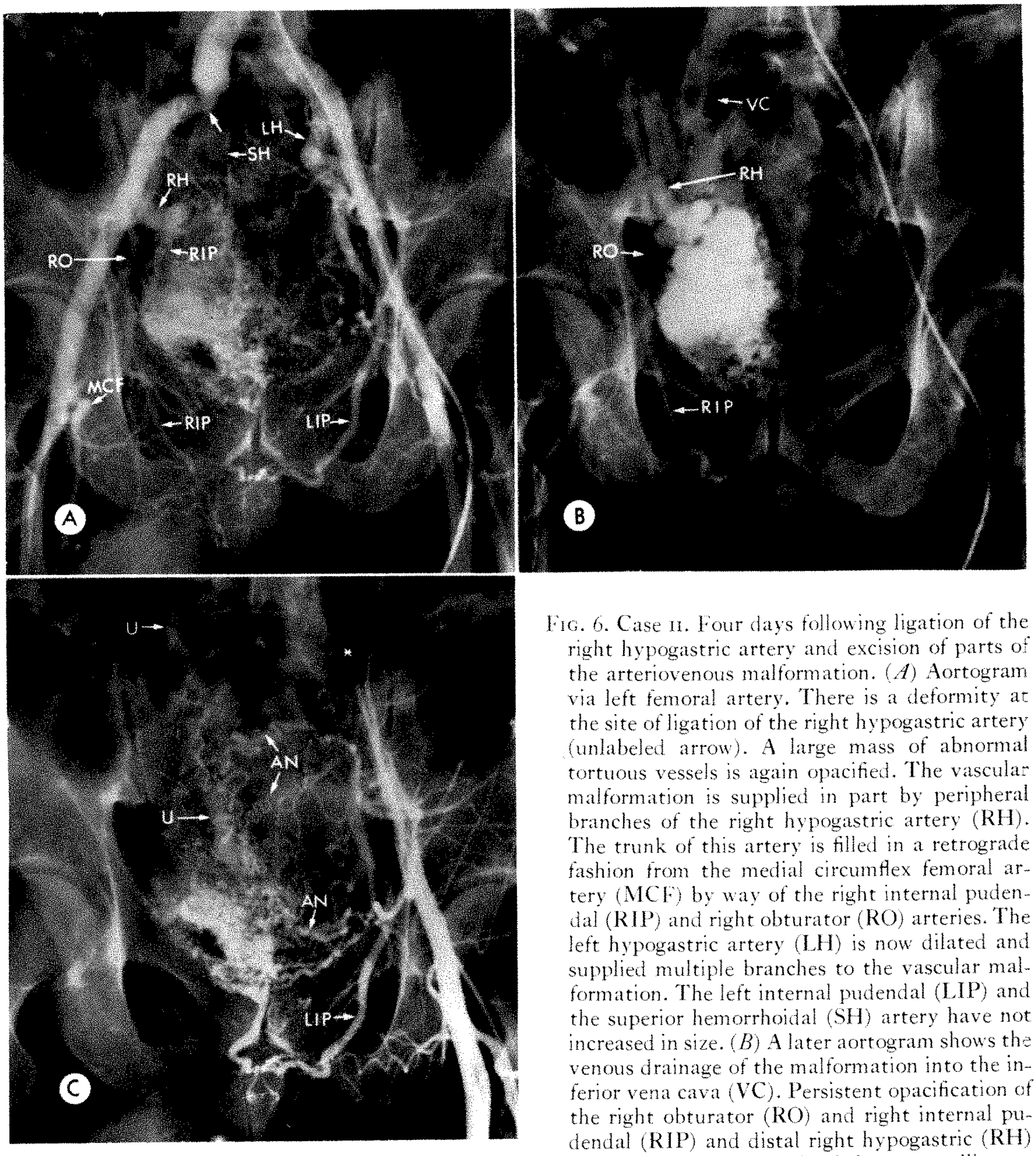
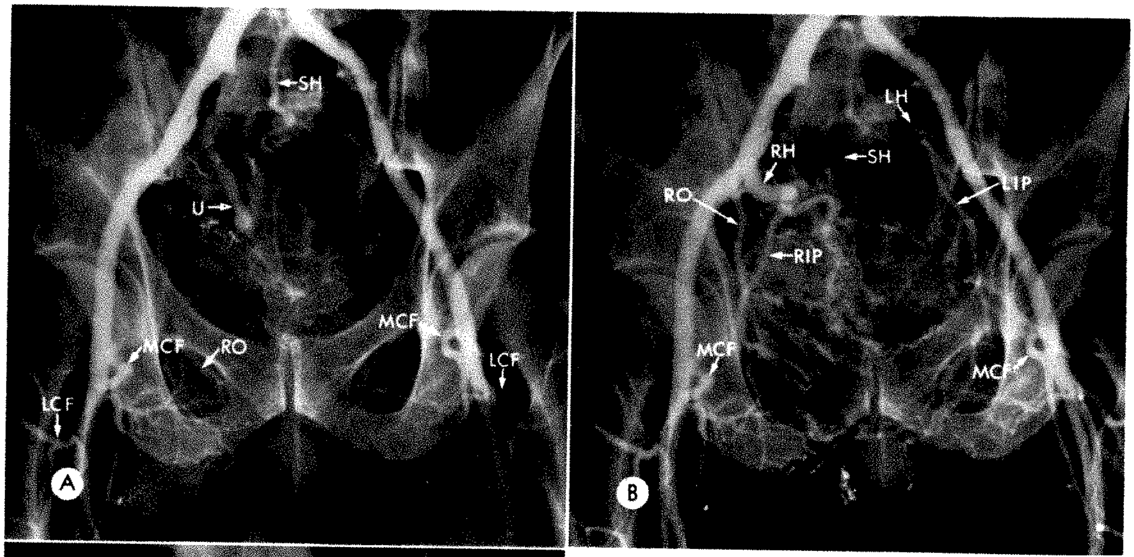


Fig. 6. Case II. Four days following ligation of the right hypogastric artery and excision of parts of the arteriovenous malformation. (*A*) Aortogram via left femoral artery. There is a deformity at the site of ligation of the right hypogastric artery (unlabeled arrow). A large mass of abnormal tortuous vessels is again opacified. The vascular malformation is supplied in part by peripheral branches of the right hypogastric artery (RH). The trunk of this artery is filled in a retrograde fashion from the medial circumflex femoral artery (MCF) by way of the right internal pudendal (RIP) and right obturator (RO) arteries. The left hypogastric artery (LH) is now dilated and supplied multiple branches to the vascular malformation. The left internal pudendal (LIP) and the superior hemorrhoidal (SH) artery have not increased in size. (*B*) A later aortogram shows the venous drainage of the malformation into the inferior vena cava (VC). Persistent opacification of the right obturator (RO) and right internal pudendal (RIP) and distal right hypogastric (RH) arteries indicates slower flow on the right side as compared to the left. (*C*) Selective left common iliac artery injection (*) demonstrates multiple dilated anastomotic channels (AN) supplying the vascular malformation. Most of the blood entering the malformation now comes from the left side. (LIP) left internal pudendal artery; (U) right ureter.

residual vascular malformation primarily from branches of the left hypogastric artery (Fig. 6, *A*, *B* and *C*).

The patient was operated on again. The left hypogastric artery was ligated as well as several of the lower lumbar arteries and all branch vessels arising from the common iliac, external iliac, and common femoral arteries. The patient was re-studied 5 days following the second operative procedure. Aortography and



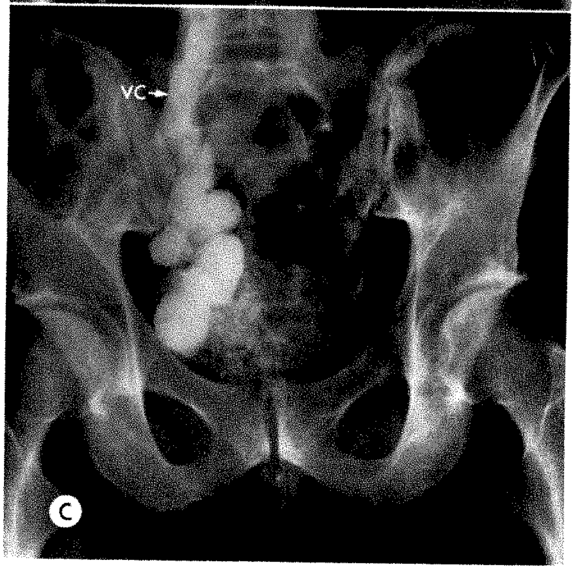


FIG. 7. Case II. Five days following ligation of the left hypogastric artery and multiple feeding vessels. Catheter aortogram via left axillary artery. (*A*) An early aortogram demonstrates dilatation of the superior hemorrhoidal artery (SH). There is faint opacification of the right obturator artery (RO) by retrograde flow from the medial circumflex femoral artery (MCF). Medial deviation of the right ureter persists (U). (LCF) lateral circumflex femoral artery. (*B*) Aortogram 1.3 seconds later shows progressive retrograde filling of the distal stump of the right hypogastric (RH) and left hypogastric artery (LH) from the medial circumflex femoral arteries (MCF). There is beginning opacification of the vascular malformation from branches of the distal hypogastric arteries and from the intact superior hemorrhoidal artery (SH). (RIP) right internal pudendal artery; (LIP) left internal pudendal artery; (RO) right obturator artery. (*C*). A later aortogram shows the venous drainage of the vascular malformation into the inferior vena cava (VC).

selective right and left iliac arteriography were performed through the left axillary artery approach. Both hypogastric arteries had been successfully ligated. The superior hemorrhoidal artery was enlarged. As the femoral arteries became opacified, the contrast medium flowed through collateral vessels from the medial circumflex femoral arteries in retrograde fashion into the pudendal and obturator arteries and then filled the distal segment of the hypogastric arteries and their branches (Fig. 7, *A* and *B*). These led into the vascular malformation in the pelvis and then drained into the inferior vena cava (Fig. 7*C*). Filling of the vascular supply of the malformation was considerably slower postoperatively. Selective right and left iliac artery injections demonstrated filling of the malformation from both femoral arteries.

The bleeding recurred following the second operation so that additional transfusions became necessary. A total of 20 units of whole blood were administered following the initial hemorrhage and the subsequent two operations. A direct abdominal approach to the bleeding point in the bladder was avoided since

there was concern that new bleeding sites might occur by surgically entering the bladder.

A third operation was performed at which time both profunda femoral arteries were ligated. Following this procedure the bleeding ceased and the patient has done well.

DISCUSSION

Congenital arteriovenous malformations may be found in any area of the body. The communications within the lesion are usually multiple and extensive, although rarely only a few arteriovenous channels are present. Usually, the dilated large arteries and veins and the associated smaller vessels form an hemangiomatous mass most likely representing an elaboration of the embryologic capillary plexus from which both arteries and veins develop.[9,10]

These malformations may produce systemic or local effects. The systemic changes have been well documented and consist of an increased cardiac output, increased blood volume, cardiac hypertrophy and a widened pulse pressure.[8] Locally, the effects are usually secondary to pressure or bleeding. When the malformation ininvolves a limb, there may be gross growth disturbances.[5]

Involvement of the bladder and ureter by pelvic aneurysms of the arteriosclerotic variety is a well known phenomenon.[6,11] Reports of congenital vascular malformations causing such changes are less common. Utz and Kincaid[11] illustrated such a case. Retrograde cystography demonstrated marked displacement of the bladder by a mass that proved to be a congenital arteriovenous fistula. Preoperative vascular studies were not presented. Frencken and Landman[4] reported angiograms in a patient with menorrhagia in which the uterus was markedly involved by a congenital vascular malformation. Recently, MacIntyre,[9] demonstrated by abdominal aortography a pelvic vascular malformation in a patient complaining of pelvic pain, a desire to defecate, and painful erection. In the cases presented in this report, the local effects were also prominent. Since the lesions were located in the pelvis, the symptoms of suprapubic pain, dysuria and frequency are not surprising. Conventional roentgenographic examinations revealed extrinsic pressure on the bladder, ureter and rectum as by a mass. The clinical evaluation of the first patient was most important in that a palpable thrill was present. This prompted the vascular study and enabled the correct diagnosis to be made. In the second patient, the evaluation of a pelvic mass with symptoms referrable to the genitourinary system prompted cystoscopy. The urologist noted the presence of pulsations of the bladder wall at the time of cystoscopy but this may be seen normally. Unfortunately, the biopsy which was attempted led to hemorrhage. It was this complication that prompted the vascular studies which led to the correct diagnosis.

Cinefluorography was not performed on these patients. It is possible that if this had been done when the bladder and ureter were opacified during urography, active pulsations of the mass might have been noted. This may be a useful screening procedure for obscure pelvic masses before biopsy or operative intervention is attempted.

Surgical treatment of these lesions is difficult since the vascular communications are usually multiple and may involve the walls of various viscera. Avoidance of elective surgery is usually advised if clinically feasible.[8,10] It is not surprising that unilateral ligation of the ipsilateral hypogastric artery was not effective in Case II in controlling the bleeding. Bilateral hypogastric and profunda femoral artery ligation became necessary along with ligation of larger local vessels within the malformation.

The collateral circulation within the pelvis is excellent. Burchell and Olson[2] have demonstrated good collateral blood flow within the pelvic vessels following

bilateral hypogastric artery ligation although the pulse pressure within the vessels is decreased. The resultant decreased flow is important in allowing a clot to form and organize at a bleeding site so that hemostasis may occur.

SUMMARY

Two young men with congenital pelvic arteriovenous malformations are reported. Both had local symptoms related to the presence of a mass. Angiographic studies were diagnostic and essential in guiding treatment.

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Case I is a patient of Dr. Alvin Tierstein. Surgery was performed by Dr. S. Crawford. Case II is a patient of Drs. E. Pader and S. Glickman.

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ARTERIOGRAPHY OF PERIPHERAL VASCULAR TRAUMA*

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DESPITE the increasing use of arteriography in the various fields of radiology, the study of peripheral vascular trauma has received relatively little attention.[3,4,6,8,9] In a large trauma center we have had numerous opportunities to make use of arteriography in the evaluation of peripheral vascular injury. Our purpose here is to present the roentgenographic findings in various types of vascular trauma as well as the indications for this diagnostic procedure. Thirteen case presentations will be preceded by a discussion of the significant pathologic, clinical, and roentgen findings.

PATHOLOGY

The most common vascular injury demonstrated in this study was an uncomplicated pseudoaneurysm. The remaining lesions consisted of traumatic thrombosis associated with an arterial laceration or contusion, and pseudoaneurysm accompanied by an arteriovenous fistula.

A pseudoaneurysm is also designated by the terms false aneurysm and pulsating hematoma. Pathologically it consists of a hematoma in direct continuity with the arterial lumen. In time the hematoma becomes surrounded by a fibrous sac derived from the organization of its peripheral layers.[1,5] The wall of a true aneurysm consists of all three layers of the normal artery (intima, media, adventitia), whereas the pseudoaneurysm wall contains only an intima which forms after the aneurysm has persisted for a considerable time. Flowing blood within a central cavity is responsible for the frequent pulsatile nature of the aneurysm. The size of the hematoma is determined by the surrounding tissue resistance, magnitude of the arterial defect, blood coagulation, and mean arterial blood pressure.[2] In long standing hematomas, calcium salts may be deposited in portions of the wall which have undergone degeneration.[1]

CLINICAL DIAGNOSIS

The clinical differentiation between uncomplicated pseudoaneurysm and pseudoaneurysm associated with an arteriovenous fistula is generally made with ease. A palpable mass which may or may not be pulsatile is present in both cases. The pseudoaneurysm, however, classically produces a systolic bruit while an arteriovenous communication presents a continuous murmur with systolic accentuation and a palpable thrill. The systemic effects of increased pulse pressure, cardiac output, blood volume, and cardiac size are observed only in arteriovenous fistulae of significant size and duration.[7] Branham's sign, a reflex slowing in the pulse rate after the shunt has been stopped by pressure on the feeding artery, is also specific for an arteriovenous fistula.[3]

It is important to remember that occasionally either condition may present as a nonpulsatile tender mass simulating an abscess, the differentiation from which is extremely important for proper treatment.

ROENTGENOGRAPHIC FINDINGS

On plain roentgenograms, 3 of our cases demonstrated a well circumscribed soft tissue mass which arteriographically was an obvious pseudoaneurysm. The presence of calcification within the mass and secondary periosteal reaction both indicate the

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chronicity of the process (Fig. 13, *A* and *B*).

In 2 cases of traumatic thrombosis, arteriography demonstrated a block to the flow of the contrast medium. The proximal end of the thrombus may be identified when a convex filling defect occurs in the distal column of the contrast medium (Fig. 2). Definite collateral vessels could be seen 3 hours after the initial trauma (Fig. 1).

The characteristic arteriographic finding of a pseudoaneurysm is prolonged visualization of the extraluminal sac due to stagnant blood circulation. The true size of a pseudoaneurysm is not indicated by the visualized sac alone but also by the magnitude of the surrounding nonopacified hematoma. The size of the hematoma may be estimated if there is any visible displacement of adjacent vessels. Case VIII shows a 2 cm. opacified aneurysmal sac with a nonopacified mass displacing small vessels at a considerable distance from the sac (Fig. 8). At surgery 2,800 cc. of surrounding hematoma was found. We have also noticed that there is frequent compression of the injured vessel by the pseudoaneurysm, with no compromise in the distal flow of the contrast medium. This accounts for the clinical finding of persistent peripheral pulses in cases of pseudoaneurysm. Varying densities within the opacified sac represent eddy currents (Fig. 10). Occasionally, radiolucent areas caused by adherent clots can be visualized (Fig. 13*C*).

The arteriographic diagnosis of traumatic arteriovenous fistula is easily made and has recently been discussed by Bell and Cockshott.[3] Our 3 cases were all associated with pseudoaneurysms, 1 of which originated from a vein. Some of the secondary physiologic changes of an arteriovenous fistula were demonstrated in Case XIII. The proximal artery and vein were both dilated beyond their normal size. Retrograde venous flow resulting from increased venous pressure and incompetent valves was noted, and manifested clinically by a prominent superficial venous pattern on the leg (Fig. 13*C*).

REPORT OF CASES

The following case presentations are subdivided according to the time elapsing between the initial injury and a definitive diagnosis; they are thus classified as acute, subacute, or chronic.

ACUTE

CASE I.—L. J., a 32 year old Negro male, was shot in the right knee 3 hours prior to admission. The patient noted a cool sensation in the right leg. Physical examination revealed absent pulses distal to the knee and coolness of the toes. Femoral arteriography demonstrated a block in the distal popliteal artery (Fig. 1). Minimal collateral circulation via the inferior genicular arteries was already apparent. Surgery revealed nearly complete transection of the distal popliteal artery with a thrombus occluding the lumen at this site. The damaged arterial segment was resected.

CASE II.—L. C., a 47 year old Negro male, sustained a gunshot wound to the right knee 6 hours prior to admission. On physical examina-

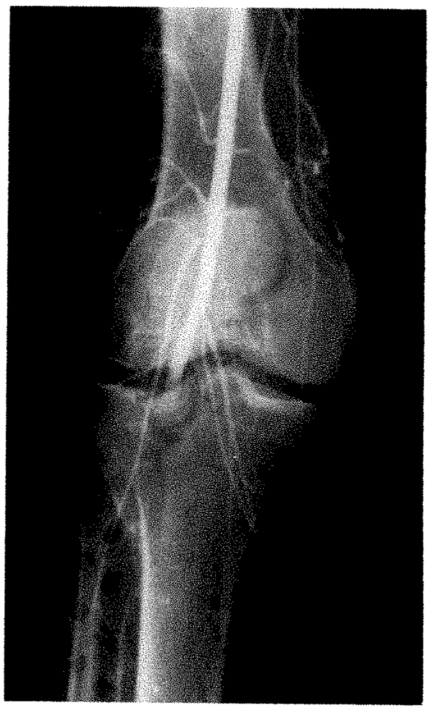

FIG. 1. Case I. Occlusion of the right popliteal artery. Collateral circulation via the inferior genicular arteries is seen 3 hours after the initial injury.

tion there was no palpable pulse distal to the right knee, and the right foot was cool. Femoral arteriography revealed a complete block in the popliteal artery (Fig. 2). The distal end of the contrast medium demonstrated a convex filling defect. Surgery revealed a contusion of the distal popliteal artery which also contained a thrombus. The contused segment of the vessel was resected.

Case III.—L. G., a 21 year old Negro male, was shot in the left subclavicular area 12 hours preceding admission. Initial examination showed only a hematoma overlying the left pectoralis major. The arteriogram revealed a pseudoaneurysm of the left axillary artery at the origin of the subscapular branch (Fig. 3). Surgery demonstrated a 2 cm. tangential laceration of the axillary artery along with the resulting pseudoaneurysm. The lacerated arterial segment was resected and the hematoma evacuated.

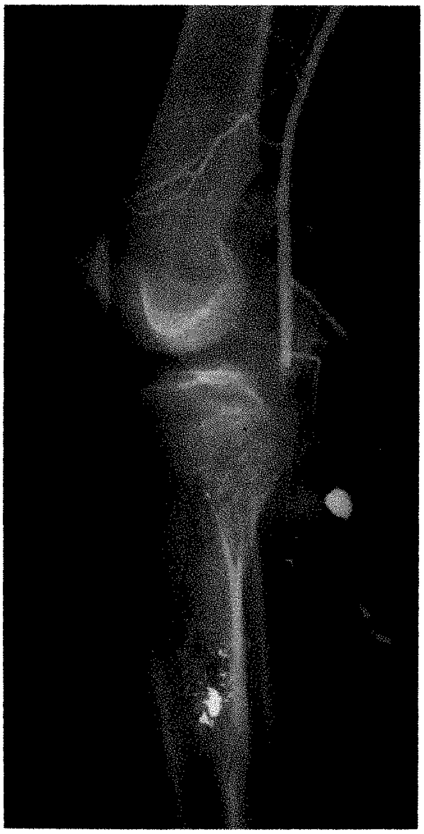

Fig. 2. Case II. Complete occlusion of the right popliteal artery with the occluding thrombus outlined by a convex filling defect.

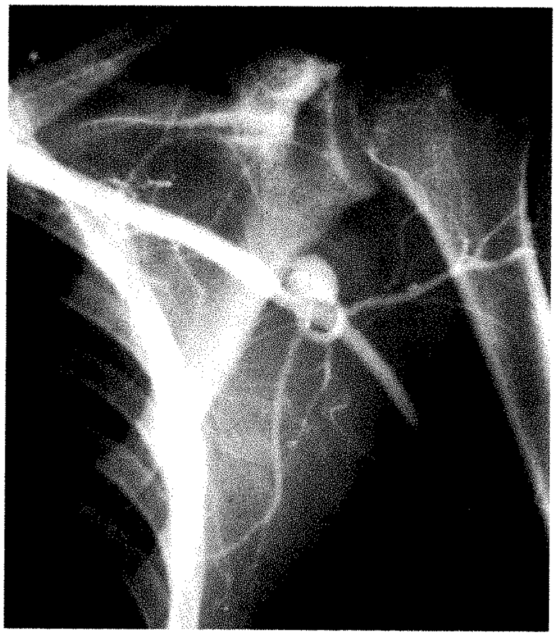

Fig. 3. Case III. Two seconds after injection of contrast medium. Pseudoaneurysm of the left axillary artery at the origin of the subscapular branch.

Case IV.—M. W., a 15 year old Negro male, was stabbed in the right buttock approximately 24 hours before admission. When seen earlier at another hospital, the patient required 1,000 cc. of blood to control the hemorrhage. Following transfer to Cook County Hospital, a systolic bruit was heard in the right gluteal area. The peripheral pulses were normal, and no masses were palpable. The arteriographic study revealed premature visualization of the right hypogastric and common iliac veins (Fig. 4*A*). Later roentgenograms demonstrated a small collection of contrast medium which proved to be a pseudoaneurysm of the inferior gluteal artery (Fig. 4*B*). Surgery confirmed the findings of an arteriovenous communication and associated pseudoaneurysm of the inferior gluteal vessels, and the fistula and injured arterial segment were excised.

Case V.—M. J., a 33 year old Negro female, was shot in the mouth 4 hours prior to admission. Skull roentgenograms revealed that the bullet was located inferior to the right petrous pyramid, and thus carotid arteriography was done to evaluate the status of the internal carotid artery. The study demonstrated a pseudoaneurysm in the prepetrosal portion of the internal carotid artery (Fig. 5). Surgery re-

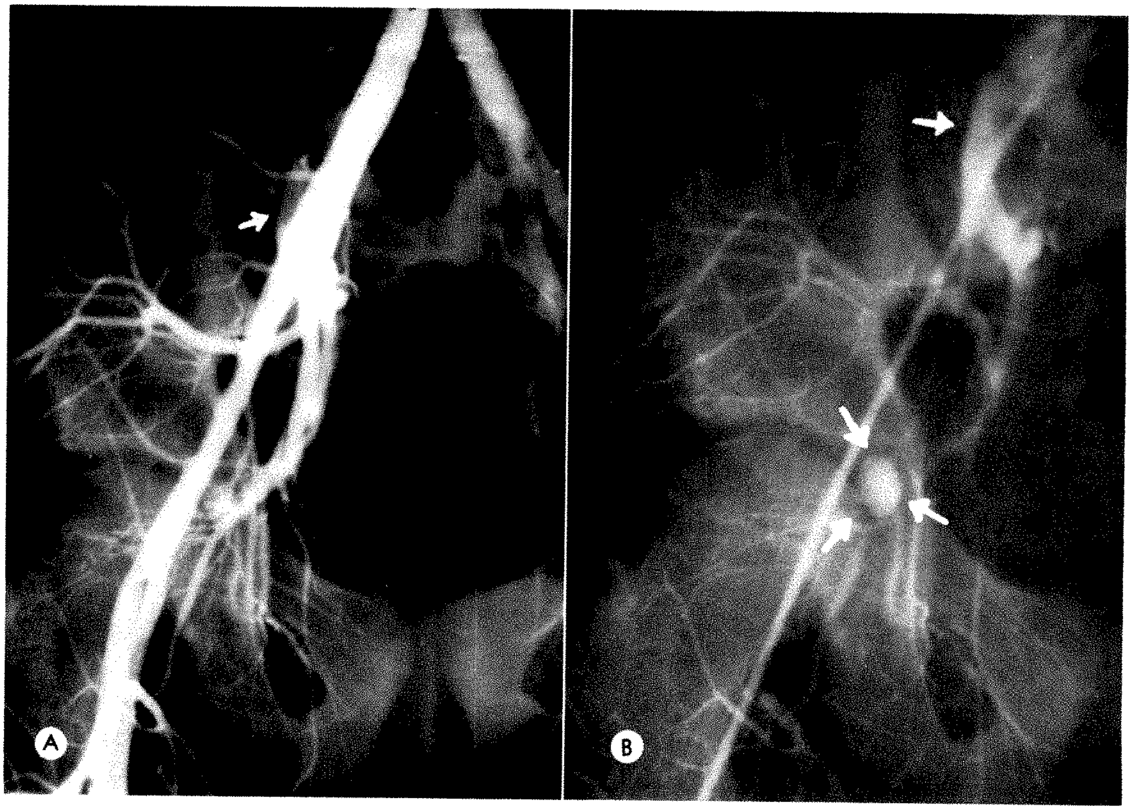

Fig. 4. Case iv. (*A*) Two seconds. Premature visualization of the right hypogastric and common iliac veins. (*B*) Three seconds. Small pseudoaneurysm originating from the inferior gluteal artery with visualization of the inferior vena cava.

vealed such an extensive laceration of the vessel that it had to be ligated.

SUBACUTE

Case vi.—D. F., a 42 year old Negro male, was stabbed just below the right knee 1 month prior to admission. Three weeks after the initial trauma, the patient noticed a pulsating mass in the same area. On physical examination a continuous murmur was heard over a 1 cm. pulsatile mass, while the peripheral pulses were normal. Arteriography demonstrated early visualization of the popliteal vein associated with a large bilobed pseudoaneurysm; this was subsequently found to originate in the anterior tibial vein (Fig 6). A 1 mm. communication between the anterior tibial artery and vein was visualized at surgery.

Case vii.—J. W., a 52 year old Negro male, received multiple stab wounds in the right forearm 3 months before admission, and had noticed an enlarging painful mass for 2 weeks. Physical examination revealed an orange size nonpulsatile mass on the volar surface of the proximal right forearm. A systolic bruit was heard over the area, and the peripheral pulses were normal. A soft tissue mass was visualized in the early phases of the arteriography, while later arteriograms demonstrated the mass to be a large pseudoaneurysm arising from the proximal radial artery (Fig. 7, *A* and *B*). The findings were confirmed during surgery, where the hematoma was evacuated and the damaged arterial segment resected.

Case viii.—L. S., a 35 year old white male, sustained a subtrochanteric fracture of the right femur in an automobile accident. The fracture was fixed with a Smith-Peterson nail and a McLaughlin bar. Three weeks later the patient noted pain in the right thigh, the medial aspect of which was indurated on palpation. The patient was thought to have an abscess, but a needle aspiration yielded only blood. After a 2 week interval with no significant

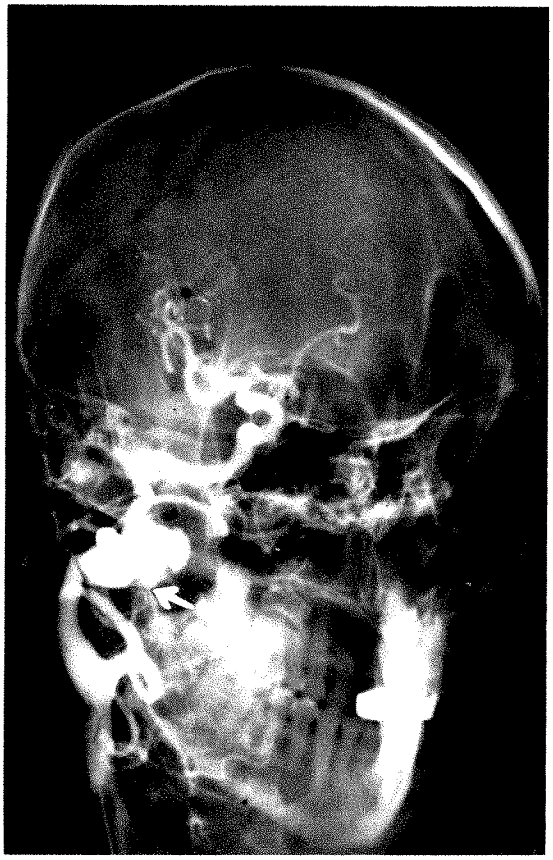

FIG. 5. Case V. Pseudoaneurysm originating from the prepetrosal portion of the right internal carotid artery.

FIG. 6. Case VI. Two seconds. Premature visualization of the right popliteal vein with a large bilobed pseudoaneurysm of the anterior tibial vein.

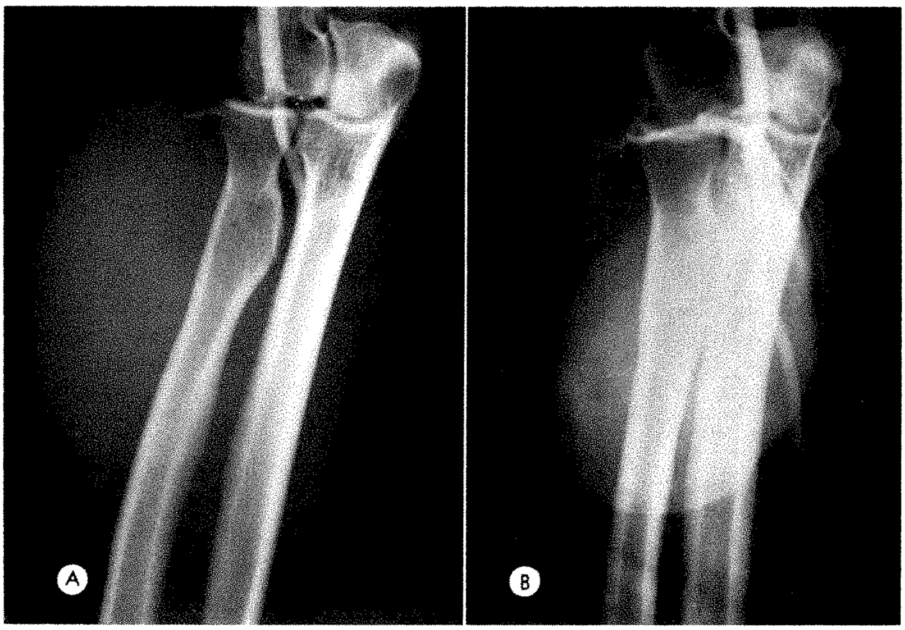

FIG. 7. Case VII. (*A*) Large soft tissue mass noted on the volar surface of the right forearm. (*B*) Arteriography demonstrates the mass to be a pseudoaneurysm arising from the proximal radial artery.

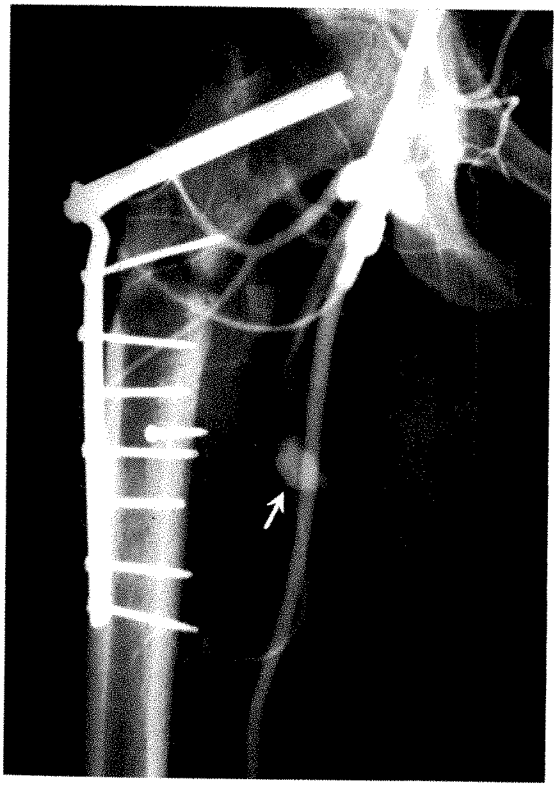

FIG. 8. Case VIII. Small opacified sac of a pseudoaneurysm of the right deep femoral artery. Note the large nonopacified hematoma causing displacement of small vessels.

change, the pain increased. A pulsatile mass was now present in the medial thigh, and a systolic bruit was heard. Arteriography was performed and revealed a pseudoaneurysm of the deep femoral artery (Fig. 8). At surgery an arterial segment containing a 1 cm. defect was resected, and a 2,800 cc. hematoma evacuated from the surrounding soft tissues. The arterial injury was thought to result from laceration of the hip pinning procedure.

CASE IX.—P. O., a 28 year old Negro male, was stabbed in the lateral aspect of the left leg, 2 months prior to admission, and developed a painful swelling at the wound site 2 weeks later. On physical examination there was a nonpulsatile diffuse swelling over the lateral aspect of the left leg with a systolic bruit and normal peripheral pulses. The arteriogram demonstrated a pseudoaneurysm of the anterior tibial artery (Fig. 9). At surgery the anterior tibial artery was ligated, and a 400 cc. hematoma was evacuated.

CASE X.—V. G., a 34 year old Negro male, received a knife wound in the left forearm 1 month preceding admission and noted a painless mass 2 weeks later. Physical examination revealed a 4 cm. pulsating mass on the volar aspect of the proximal left forearm. A systolic bruit was auscultated over the mass, and the left radial pulse was moderately decreased. An arteriogram demonstrated a large pseudoaneurysm arising from and compressing the proximal radial artery (Fig. 10). The injured arterial segment, containing a 0.5 cm. defect, was resected at surgery.

CHRONIC

CASE XI.—E. S., a 28 year old white male (and known heroin addict), had recently been injecting paregoric into the left groin. One month prior to admission the patient developed

FIG. 9. Case IX. Pseudoaneurysm of the left anterior tibial artery with the nonopacified hematoma displacing both the anterior and posterior tibial arteries.

pain and swelling in the groin and was treated by a physician for an infection. The symptoms became progressively severe, and by the time of hospital admission, a 12 by 20 cm. nonpulsating mass was palpable in the left groin. A systolic bruit was audible over the mass. The peripheral pulses were normal. The initial arteriogram revealed a large pseudoaneurysm arising from and compressing the common femoral artery (Fig. 11*A*). Following surgical ligation of the left external iliac artery, there was a significant decrease in the size of the aneurysm (Fig. 11*B*). Definitive surgery consisted of evacuating a 1,000 cc. hematoma and resecting a segment of the common femoral artery containing a 1 cm. defect.

Case xii.—J. L., an 84 year old Negro male, had sustained a gunshot wound in the right shoulder 15 years previously. The patient had noted a gradually increasing weakness of the right arm for several years, but was unaware of any mass. On physical examination a pulsating mass, over which was heard a systolic bruit, was palpable in the right axilla. The peripheral pulses were normal. Arteriography revealed a large pseudoaneurysm of the axillary artery, which was not treated surgically (Fig. 12).

Fig. 10. Case x. Seven seconds. Prolonged visualization of a pseudoaneurysm arising from the right radial artery. Varying densities within the opacified sac represent eddy currents.

Case xiii.—A. V., a 43 year old Negro male, received a traumatic laceration of the left leg 10 years prior to admission. Several weeks following the initial injury, the patient noticed a swelling at the wound site which gradually enlarged throughout the years. Physical examination revealed a 3 cm. nonpulsatile mass on the medial aspect of the left distal thigh. A continuous murmur was auscultated over the area. Additional findings included dilated superficial veins over the left leg, mild ankle edema, and Branham's sign. The peripheral pulses were normal. Roentgenographic studies revealed a calcified soft tissue mass in the left distal thigh associated with periosteal reaction of the adjacent femur (Fig. 13, *A* and *B*). The femoral arteriogram demonstrated an arteriovenous fistula of the femoral vessels (Fig. 13*C*). The calcified mass proved to be a pseudoaneurysm of the superficial femoral artery. At surgery the fistula and damaged arterial segment were resected.

COMMENT

In the course of reviewing these case histories, several important clinical observations become apparent.

1. Our patients in the subacute group demonstrate a time interval of at least 2 weeks from the initial trauma to the presenting symptom.
2. On physical examination a mass could be palpated in all cases of pseudoaneurysm occurring in the subacute and chronic groups; however, in only 50 per cent of instances was the mass pulsatile.
3. A systolic bruit was auscultated in 6 of 8 cases of uncomplicated pseudoaneurysm, while a continuous murmur was present in 2 of 3 cases where

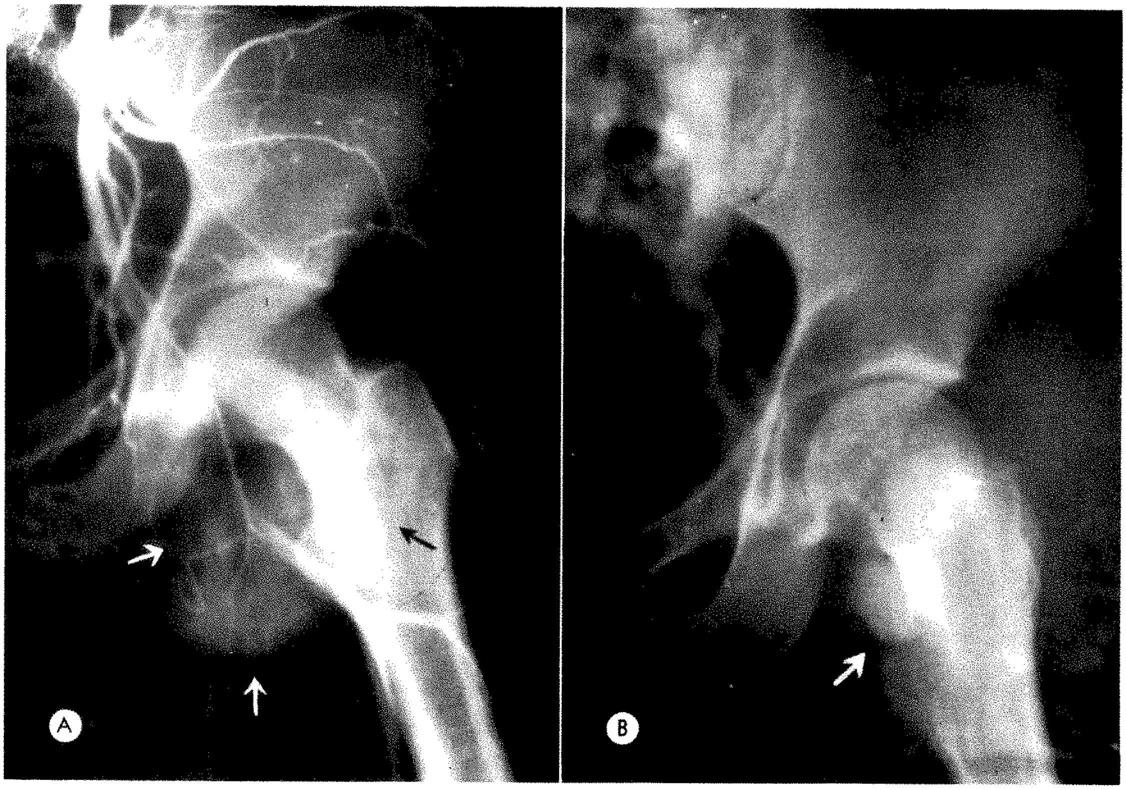

Fig. 11. Case xi. (*A*) Two seconds. Initial arteriogram reveals a large pseudoaneurysm originating from and compressing the left common femoral artery. (*B*) Eight seconds. Following surgical ligation of the left external iliac artery, note significant decrease in size of the extraluminal sac.

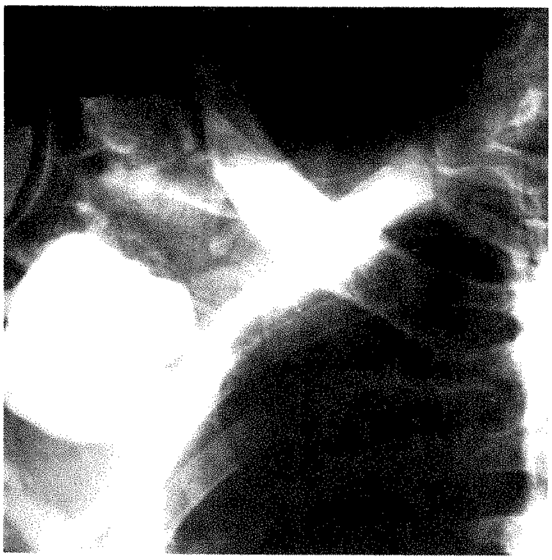

Fig. 12. Case xii. Ten seconds. Right axillary artery pseudoaneurysm with prolonged retention of contrast medium.

an arteriovenous fistula was also present. It is noteworthy that the only cases not demonstrating the classical auscultatory findings occurred in the acute group and were diagnosed within 24 hours of the initial trauma.

4. The peripheral pulses were normal in all cases of pseudoaneurysm and arteriovenous fistula with one exception, Case x.

INDICATIONS FOR ARTERIOGRAPHY

In our studies of peripheral vascular trauma, we have found arteriography to be most valuable when performed for the following indications.

1. *Localization of the Site and Extent of Arterial Injury in Patients With a Pulse Deficit.* In the presence of a

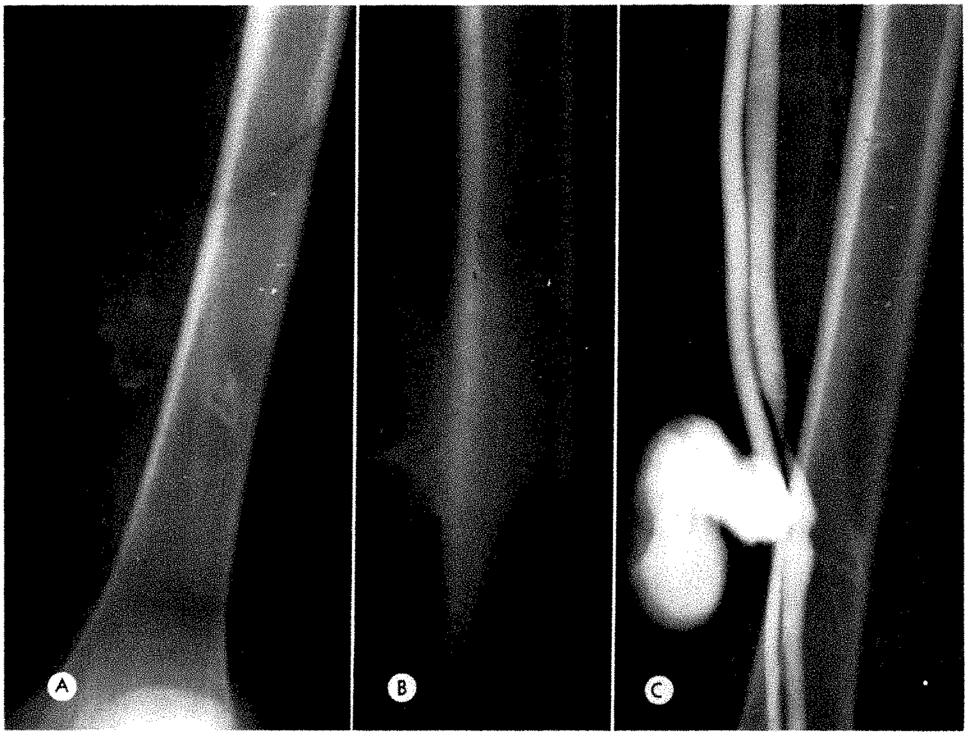

Fig. 13. Case XIII. (*A*) Calcified soft tissue mass in the media aspect of the left distal thigh. (*B*) Adjacent femur exhibits periosteal reaction. (*C*) Three seconds. Arteriogram reveals an arteriovenous fistula of the femoral vessels associated with a pseudoaneurysm of the superficial femoral artery. Note the dilated proximal vessels, retrograde venous flow, and constriction of the femoral vein caused by surrounding organized hematoma. Several radiolucencies within the sac represent adherent clots.

pulse deficit it is necessary to distinguish arteriospasm from disruption or thrombosis. One must also evaluate collateral flow and the status of the vessels distal to the injury in planning the proper operative approach.

2. *Investigation of Suspicious Injuries in Patients Without a Pulse Deficit.* Patients come under suspicion when they present evidence of excessive bleeding or have an audible bruit at the injury site. In these particular cases arteriography is used to detect and differentiate pseudoaneurysms and arteriovenous fistulae.
3. *Differentiation of Post-traumatic Swelling.* The development of a painful nonpulsatile mass several weeks following trauma may clinically resemble an abscess. Since the presence of a systolic bruit does not rule out this possibility, arteriography is necessary for appropriate diagnosis and management.
4. *Establishment of an Accurate Preoperative Diagnosis in Cases where Diagnostic Clinical Findings are Lacking.* In our material this condition applied to acute cases where there was insufficient time for the findings to develop.

SUMMARY

Thirteen cases of peripheral vascular trauma were evaluated with the use of arteriography. There were 2 cases of traumatic thrombosis and 11 pseudoaneurysms, 3 of which were associated with arteriovenous fistulae.

A brief discussion of the significant pathologic and clinical findings is presented.

The characteristic arteriographic finding in pseudoaneurysm is prolonged visualization of the extraluminal sac, the size of which may be considerably less than that of the surrounding hematoma.

The indications for the use of arteriography in cases of peripheral vascular trauma are stated.

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THE EFFECT OF CARDIAC CATHETERIZATION AND ANGIOCARDIOGRAPHY ON THE COAGULATION ACTIVITY OF THE BLOOD*

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THROMBOEMBOLIC complications of two types may occur during catheterization procedures. One is local thrombosis at the site of the introduction of the catheter in the peripheral vessel. This complication varies in frequency in different series[3,4] and is at least partly related to the degree of trauma to the vessel locally. The other complication is formation of thrombi in the catheter or at the tip of the catheter. The thrombotic material may become detached during manipulation of the catheter or during injections of the contrast medium and produce embolism. This is fortunately rare, but cerebral embolism in particular is a very serious complication; sometimes repeated clotting in the catheter prevents the catheterization procedure. The mechanism responsible for this hypercoagulability in some patients is poorly understood. The possibility of a primarily disturbed coagulation activity in some patients must be considered; it is also conceivable that the catheterization procedure itself may cause increased coagulation activity. *In vitro* tests by Bartley, Fondberg and Jacobsson[1] demonstrated that the presence of the different catheter material in the blood produced a considerable increase in the coagulation activity. It is also known from intracardiac prostheses that presence of a plastic device in the blood stream may increase coagulation activity and lead to thrombus formation on the surface of the device.[8] It was therefore considered of interest to determine the coagulation activity in cardiac patients and to study its variations after cardiac catheterization and angiocardiography.

MATERIAL

The material consisted of 38 unselected adult cardiac patients routinely examined for cardiac disease by cardiac catheterization and angiocardiography. There were 23 men and 15 women. Their ages ranged from 21 to 65 years. The mean age was 49 years.

METHODS

In all patients cardiac catheterization of the right and/or left heart was performed. For catheterization of the right heart, NIH-catheters introduced from a peripheral vein, usually in the arm, were used. For catheterization of the left side, the transseptal technique with percutaneous introduction of a teflon catheter was used in 10 cases; in 30 cases, a retrograde catheterization of the left ventricle was performed employing a percutaneously transfemorally introduced Ödman Ledin catheter. The catheterization time varied from 15 to 360 minutes (average, 125 minutes). The dose of contrast medium (isopaque 60 per cent) for angiocardiography varied from 0.6 to 3.8 ml./kg. body weight, and the number of injections from 1 to 5. In most patients the injections were made only in the left side of the heart; however, in 5 patients the injections were made only in the right side of the heart, and in 2 cases both in the right and the left side.

The coagulation activity was determined in blood drawn from a peripheral vein. A special test substance (Normotest*) was used.[6,7] This substance is suitable for determining coagulation activity at normal

* Manufactured by Nygaard & Co. A. S. Oslo.

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levels, whereas Trombotest[6,7] is used for determinations in patients on anticoagulant treatment. Trombotest and the agent employed here permit a combined determination of changes in both the external and the internal coagulation system. The coagulation activity was determined before the catheterization, after the catheterization, immediately before the angiocardiography, and 5 minutes, 15 minutes and 4 hours after angiocardiography. In a few cases the coagulation activity was also determined 24 hours after the angiocardiography.

In all patients the degree of intravascular aggregation was determined from microphotographs of the conjunctival vessels before the catheterization, after the catheterization, and 15 minutes after the angiocardiography by a technique previously described.[2]

RESULTS

The changes in coagulation activity were expressed in per cent of the precatheterization value, and only variations of more than 10 per cent were considered significant. An increase in coagulation activity after the catheterization procedure was seen in 50 per cent of the patients, 29 per cent had a moderate decrease in coagulation activity, and in 21 per cent it remained unchanged (Table I). After angiocardiography, 77 per cent of the patients had a decrease in coagulation activity, whereas in 21 per cent it remained unchanged. An increase was seen only in 1 patient.

The three types of changes occurring in coagulation activity in different patients are illustrated in Figure 1, *A*, *B* and *C*. The first patient (Fig. 1*A*) had a considerable increase in coagulation activity during the cardiac catheterization procedure. After angiocardiography there was an immediate drop in the coagulation activity and then a return to normal 4 hours after the angiocardiography. In the second patient (Fig. 1*B*), the catheterization procedure produced no significant change in the coagulation activity. However, after angiocardiography there was a rapid decrease and a return to the original value 4 hours after the angiocardiography. The third patient (Fig. 1*C*) had a moderate decrease in coagulation activity after catheterization, a further decrease after angiocardiography, and then a slow return to normal value after 4 hours. The increase in coagulation activity varied considerably. Fourteen of the 19 patients had an increase of 30 per cent or more.

Table I

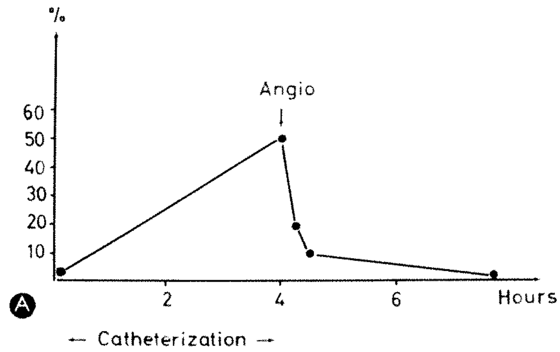
COAGULATION ACTIVITY IN 38 CARDIAC PATIENTS

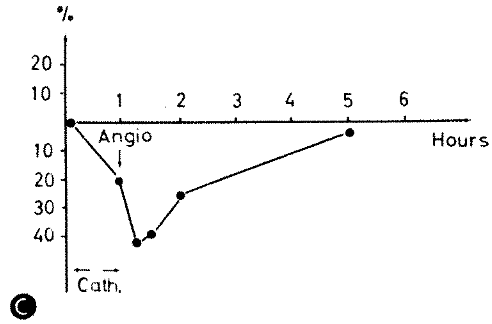
	Increased	Decreased	Unchanged
After catheterization	19 (50%)	11 (31%)	8 (19%)
After angiocardiography	1	29 (78%)	8 (19%)

DISCUSSION

The catheterization procedure produced a considerable increase in the coagulation activity in some patients but the individual response varied and in 11 patients a moderate decrease was observed. When these 11 patients were compared with the 14 patients who had a more than 30 per cent increase in coagulation activity, it was found that there was no difference in length of the catheterization procedure or number and type of catheters used between the two groups. Different hemodynamic studies at rest and at graded physical work during the catheterization made no observable difference.

There was a predominance of women in the group who had increased coagulation activity after catheterization. Nine of the total of 15 women were in this group and only 2 were in the group with decreased coagulation activity. Of the 9 women, 5 were in the menopause and 4 in the fertile age. Only 1 of them was using oral contraceptives. These findings are in agreement with the previous observation that women are more prone to develop thrombosis than men.





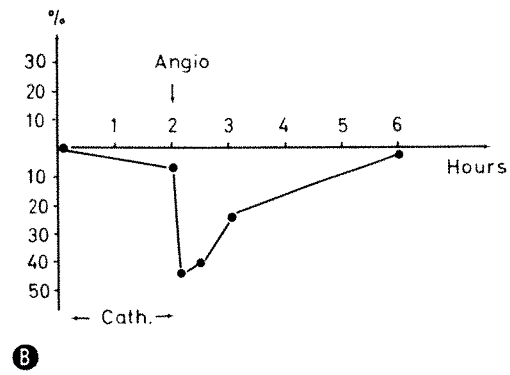


Fig. 1. Changes in coagulation activity of the blood after cardiac catheterization. (*A*) Increase in 50 per cent of patients. (*B*) No change in 19 per cent. (*C*) Decrease in 31 per cent. After angiocardiography there was a decrease in coagulation activity in 78 per cent of the patients.

When the clinical and laboratory data of the patients in the "increase" and "decrease" groups were compared, no obvious difference was found. An increased blood sedimentation rate was noted in 1 patient in each group, the hematocrit was slightly increased in 2 cases in each group. One patient with increased coagulation activity had an abnormally high gamma globulin value. Nine patients in the "decrease" group and 3 in the "increase" group had received prophylactic oral penicillin 24–48 hours before the catheterization. Oral penicillin could change the number and type of bacteria in the intestine, thus disturbing the production and absorption of vitamin K, which could influence the coagulation activity of the blood. However, the precatheterization values of coagulation activity were no different in one group than in the other, and it was not possible to predict from these values whether an increase or decrease would occur after catheterization.

The intravascular aggregation, as observed on photographs of the conjunctival vessels, was much more pronounced in patients with an increase in coagulation activity after the catheterization than in patients who had a decrease in the coagulation activity (Table II). In the first group, increase in sludge occurred in 6 cases during the catheterization, whereas this was seen only in 2 cases in the second group. The mechanism of the changes in coagulation activity during cardiac catheterization remains obscure. The influence of the catheter material can only be one of several

Table II

Intravascular Erythrocyte Aggregation in Conjunctival Vessels in Correlation to Changes in Coagulation Activity after Cardiac Catheterization

Coagulation Activity	Degree of Sludge			
	0	+	++	+++
Increased >30%	1	1	7	5
Decreased	5	5	1	—

factors, and the very marked changes found *in vitro* by Bartley *et al.*[1] were not seen in our group of patients. The stress of the procedure and the injury to vessels by the introduction of catheters may increase the coagulation activity. The degree of stress could not be measured, however, and there were no obvious differences in the degree of injury to the vessels in various patients.

The decrease in coagulation activity, noted in nearly 80 per cent of the cases, occurred very rapidly after the injection of the contrast medium and was maximal in 5 minutes. This rapid decrease could partly be explained by the hemodilution known to occur after injection of the hypertonic contrast media into the blood,[2] as there was a fairly good correlation between the decrease in hematocrit and the coagulation activity. The coagulation factors are proteins, and it is conceivable that the binding of contrast medium to them[5] could temporally inactivate them.

A more direct toxic effect of the contrast medium on the coagulation factors cannot be excluded; however, the rapid return to normal values within 4 hours makes mechanisms such as proteinbinding and hemodilution the more likely explanations.

In 2 patients with markedly increased coagulation activity after catheterization, clotting in the catheter occurred. In 1 patient the catheter was removed and the examination was uneventfully completed with a new catheter. In the second patient a transseptal teflon catheter became clotted and, while it was being removed, the patient suddenly developed neurologic symptoms from the fifth and seventh cranial nerves on the left side. The symptoms were only slight, however, and disappeared after 15 minutes. On examination of the catheter, it was found to contain blood clots along most of its length. At the tip there were small fibrinous clots on the outside of the catheter; it is probable that one of these had become detached causing a small cerebral embolus. No other complications of a thrombotic nature, either coagulation in the catheters or thrombosis at the site of introduction in the peripheral vessels, occurred.

It is obvious that a considerable increase in coagulation activity, combined occasionally with clinically detectable thromboembolism, may occur in patients during cardiac catheterization. It is difficult to predict in which patients this might occur, but patients with evidence of increased intravascular aggregation, and particularly women, are more prone to develop this complication than others. On the other hand, the injection of contrast medium in angiocardiography generally decreases the coagulation activity and thus counteracts the increase caused by the catheterization procedure. One thus may say that, as regards the risk of thromboembolism, it is hazardous to perform cardiac catheterization but advantageous to inject contrast medium for angiocardiography.

SUMMARY

In a series of 38 patients, the coagulation activity of the blood after cardiac catheterization increased in 19 cases (50 per cent); decreased in 11 cases (29 per cent); and remained unchanged in 8 cases (21 per cent).

Angiocardiography produced a rapid decrease in coagulation activity in 29 patients (77 per cent).

The increase in coagulation activity after cardiac catheterization occurred more frequently in women than in men and was correlated to increased intravascular aggregation but not to other clinical or laboratory data.

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ENZYME ACTIVITY FOLLOWING ANGIOGRAPHY*

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ELEVATED activity of serum glutamic oxaloacetic transaminase (SGOT) after cardiac catheterization and angiography has been reported to occur in 8 to 44 per cent of the cases.[1,7] An abnormal elevation of SGOT after cardiac catheterization was noted by Taquini *et al.*[7] in 1 of 13 patients undergoing right heart catheterization (8 per cent), but in 25 per cent subjected to transseptal left heart catheterization. A significant increase in transaminase activity within 24–48 hours was found by Adrouny and associates[1] in 11 of 25 patients (44 per cent) undergoing cardiac catheterization without contrast medium injection, 7 being transseptal, and in 7 of 21 patients (33 per cent) having angiocardiography only. In 4 patients elevation was not seen until 48 hours after catheterization or angiography.

Since SGOT is known to be elevated in many disease states other than myocardial injury, it is possible that liver injury due to congestive heart failure or other cause might account for the relatively high incidence of increased SGOT following angiography. The purpose of this study was to measure not only SGOT activity but also lactic dehydrogenase (LDH), alpha-hydroxy-butyric dehydrogenase (SHBD), and creatine phosphokinase (CPK) under similar conditions, since LDH and SHBD are less affected by liver cell injury; and CPK not at all.

MATERIALS AND METHODS

One hundred and thirteen patients undergoing angiography had 818 enzyme determinations. All patients were hospitalized during the study. Patients severely ill with heart disease, but without constrictive pericarditis or shock, were studied. The activities of serum glutamic oxaloacetic transaminase (SGOT), lactic dehydrogenase (LDH), alpha-hydroxy-butyric dehydrogenase (SHBD) and creatine phosphokinase (CPK) were determined just before and 24 hours after the angiographic studies by usual methods.[2,3,4,8] The blood samples obtained from the patients were immediately centrifuged and the sera kept frozen at $-10°$ C. in the refrigerator for up to 3 days, unless the analyses were done at once, but all CPK determinations were carried out immediately. Normal activity by the methods employed were 5–40 units for SGOT, 100–600 units for LDH, 120–200 units for SHBD and 0–12 units for CPK. Borderline elevation was defined as 41–50 units for SGOT, 601–700 units for LDH, 201–260 units for SHBD, and 13–20 units for CPK.

The following angiographic procedures were performed using techniques previously published.[5,6] Twenty-nine patients had percutaneous intravenous angiocardiography, 17 patients transfemoral aortography, 9 transaxillary aortography, 8 transfemoral arteriography, 6 transaxillary arteriography, 19 selective renal arteriography, 20 selective coronary arteriography, 12 left ventriculography, 1 right ventriculography, and 3 inferior vena cavagraphy. In contrast to previously reported studies, none of the patients in this study had transseptal catheterization. The contrast media were: Renografin 60 (methylglucamine diatrizoate); Angioconray (sodium iothalamate); Hypaque, 50 per cent or

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Table I

PERCENTAGES OF PATIENTS WITH ALTERED ENZYME ACTIVITY AFTER ANGIOGRAPHY

	SGOT %	LDH %	SHBD %	CPK %
Group 1				
Borderline changes	4.1	4.8	4.9	2.9
Significant changes	—	2.9	1.9	1.9
Group 2				
Borderline changes	—	1.9	2.9	0.9
Significant changes	2.0	2.9	1.9	—
Group 3				
Borderline changes	3.1	1.9	2.9	2.9
Significant changes	—	1.9	2.9	0.9
Group 4				
Borderline changes	5.1	0.9	6.8	—
Significant changes	2.0	0.9	3.9	—
Group 5	37	36	32.2	20.1
Group 6	12.2	8.7	5.8	5.8

SGOT=serum glutamic oxaloacetic transaminase; LDH=lactic dehydrogenase; SHBD=alpha-hydroxy-butyric dehydrogenase; CPK=creatine phosphokinase.

75 per cent (sodium diatrizoate); or Isopaque (sodium, calcium, magnesium, and N-methylglucamine salts of metrizoic acid). The amount of contrast material injected varied from 20 to 300 ml. per patient.

RESULTS

The 113 patients were divided into 6 groups as listed in Table 1.

Group 1 included patients with normal levels before and borderline or clearly abnormal enzyme activity after the procedure. In this group, SGOT was borderline in 4 out of 98 patients (4.1 per cent) but no patients showed significant elevation of enzyme activity (over 50 U.) after the procedure. LDH was borderline in 5 out of 105 patients (4.8 per cent) and significantly elevated (over 700 U.) in 3 patients (2.9 per cent). SHBD was borderline in 5 out of 103 patients (4.9 per cent) and significantly elevated (over 260 U.) in 2 patients (1.9 per cent). CPK was borderline in 3 out of 104 patients (2.9 per cent) and significantly elevated (over 20 U.) in 2 patients (1.9 per cent). One of the patients had gangrene of the right foot, which may have contributed to the increased CPK activity.

Group 2 included patients with abnormal enzyme activity before but normal enzyme levels after the procedure. Among these patients, SGOT was significantly elevated (50 U. and more) in 2 out of 98 patients (2 per cent). LDH was borderline in 2 out of 105 patients (1.9 per cent) and reverted from clearly abnormal to normal values in 3 patients (2.9 per cent). SHBD was borderline in 3 out of 103 patients (2.9 per cent) and reverted to 200 U. after the procedure, but was significantly elevated in 1 patient returning to 200 U. after the procedure (0.9 per cent). CPK was borderline in 1 out of 104 patients (0.9 per cent) returning to 12 U. after the procedure.

Group 3 included patients with abnormal enzyme activity both before and after angiography, but with additional elevation in activity after the procedure. Three out of 98 patients (3.1 per cent) developed borderline increase in SGOT activity of less than 12 U. LDH activity increased

50 U. or less in 2 out of 104 patients (1.9 per cent) and in 2 (1.9 per cent) an increase in activity of 150 U. or more was seen. Insignificant elevation of 50 U. or less of SHBD appeared in 3 out of 103 patients (2.9 per cent) but an increase of 60 U. or more was found in 3 patients (2.9 per cent), one with lymphoma. An insignificant increase in CPK activity of 3 U. or less after the procedure was seen in 3 out of 104 patients (2.9 per cent) but a significant increase in activity of 22 U. was recorded in 1 patient (0.9 per cent).

Group 4 showed elevated enzyme activity both before and after the procedure although with decrease in activity after angiography. In 5 out of 98 patients (5.1 per cent) there was an insignificant fall in SGOT activity of less than 18 U., but in 2 patients (2 per cent), there was a decrease in enzyme level of more than 32 U. One out of 104 patients (0.9 per cent) showed an insignificant fall in LDH activity of 20 U.; and in another patient (0.9 per cent) there was a decrease in activity from 866 to 700 units, which may also be insignificant. Seven of 103 patients (6.8 per cent) showed an insignificant fall in SHBD activity of 25 U. or less; but in 4 (3.9 per cent), there was a decrease in enzyme activity of between 60 and 188 U. No patient had elevated CPK before and after angiographic procedures and decreased enzyme level after angiography.

Group 5 included patients with normal enzyme levels both before and after angiography, but an insignificant increase in activity was noted 24 hours after the procedures. Thirty-seven per cent of the patients showed some increase in SGOT activity which, however, remained within normal limits. The same finding occurred in 36 per cent of the patients with LDH, in 32.2 per cent of the patients with SHBD, and in 20.1 per cent of the patients with CPK determinations. By definition, there was never a significant increase in enzyme activity above normal values in this group. The changes probably reflect the standard deviations of the methods employed.

Group 6 lists the patients with normal enzyme levels both before and after angiography, but who had an insignificant fall in activity after the angiographic procedures. This occurred in 12.2 per cent of the SGOT, in 8.7 per cent of the LDH, in 5.8 per cent of the SHBD, and in 5.8 per cent of the CPK determinations. Again, these probably reflect allowable ranges in methodology.

DISCUSSION

In 113 patients SGOT, LDH, SHBD and CPK activities were determined immediately before and 24 hours after angiography. In 7 patients, (6.2 per cent), one of the enzymes was significantly elevated after the angiographic procedures. This included 1 patient with lymphoma which may be responsible for the SHBD elevation, and 1 patient with gangrene of the foot, which may have contributed to the elevated CPK activity. If they are excluded, only 5 or 4.4 per cent of 113 patients showed significant increased activity of one enzyme. Three patients (2.7 per cent), had a significant elevation of two enzymes, but none had increased activity of three enzymes. Underlying disease, angiographic procedures, amount of contrast media, and enzyme activities of the 10 patients are listed in Table II. No correlation was found between changes in enzyme activity and the various diagnoses, type of angiographic procedure, radiopaque medium employed, or the quantity of contrast agent injected.

None of the patients with significant enzyme changes developed abnormal electrocardiographic changes during the period of this study and none had a major complication during angiography. Significant also was the fact that none of the 20 patients undergoing selective coronary arteriography exhibited increase in enzyme activity above the normal range.

Of the enzymes studied no significant increase in SGOT activity was found in any of the patients. Significant increase in LDH activities was noted in 4.8 per cent as well

Table II

SUMMARY OF PATIENTS WITH SIGNIFICANT INCREASE OF ENZYME ACTIVITIES AFTER ANGIOGRAPHY

Patient	Diagnosis	Procedure	Contrast Medium (ml.)	SGOT		LDH		SHBD		CPK	
				Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	RHD, MS, MI, TI	Intravenous angiocardiography, percutaneous	63 Angioconray	21	47	566	*810**	197.4	197.4	20	23
2	RHD, MS, MI	Intravenous angiocardiography, percutaneous	100 Angioconray	36	38	610	*800**	386.4	*450.8**	0	0
3	Hypertension	Aortography, retrograde transfemoral; selective renal arteriography	55 Hypaque 50% 75 Hypaque 75%	30	14	430	*880**	188.8	*394.6**	12	12
4	RHD, MS, MI	Intravenous angiocardiography, percutaneous	60 Angioconray	69	54	460	*1,000**	166	*360**	0	0
5	Abdominal aneurysm RHD, AS, AI	Aortography, percutaneous transaxillary	200 Hypaque 50% 75 Hypaque 75%	29	34	400	500	188 (hemolized)	299	26	*48**
6	Abdominal aneurysm	Intravenous aortography, percutaneous	30 Hypaque 50% 60 Angioconray	22	15	460	580	258.8	252	0	*58**
7	Pulmonary emboli	Intravenous angiocardiography, percutaneous transfemoral	40 Isopaque	19	—	610	660	293.8	*452**	10	18
8	RHD, MS, MI	Aortography, supravalvular, percutaneous transaxillary	70 Hypaque 75% 30 Hypaque 50%	48	51	666	*820**	442	442	0	0
9	Lymphoma	Arteriography, selective renal	53 Hypaque 75% 5 Hypaque 50%	29	27	900	880	440	*520**	0	0
10	Gangrene of foot	Arteriography, femoral, via percutaneous transfemoral	30 Renografin 60	25	22	340	420	180	166	5	*26*

SGOT = serum glutamic oxaloacetic transaminase; LDH = lactic dehydrogenase; SHBD = alpha-hydroxy-butyric dehydrogenase; CPK = creatine phosphokinase. RHD = rheumatic heart disease; MS = mitral stenosis; MI = mitral insufficiency; TI = tricuspid insufficiency; AS = aortic stenosis; AI = aortic insufficiency.

* The asterisks and italics denote significant changes in enzyme level.

as in 4.8 per cent for SHBD. CPK activity rose significantly in 2.9 per cent. One of the patients with significant SHBD elevation had active lymphoma and 1 with significant increase in CPK activity had gangrene of the foot. Poorly understood was the observed significant decrease of SGOT activity after angiography in 3.1 per cent, of LDH in 3.8 per cent, and of SHBD activity in 4.8 per cent.

Part of the elevations in SGOT, LDH and SHBD activities could be due to centrolobular liver injury due to congestive heart failure, and part of increased CPK activity to skeletal muscle damage. Hemolysis of minor degree may have been responsible for increases in LDH and SHBD. It is possible that minor and transitory SGOT or CPK elevations developed before blood samples were taken 24 hours after the procedure.

After the angiographic procedures, more patients showed an insignificant increase in enzyme activity without exceeding the normal range than showed a decrease in enzyme activity. These changes in enzyme levels are probably of no importance since all activities remained within the normal range.

SUMMARY AND CONCLUSIONS

No significant increase in SGOT was observed following angiography in a series of 113 patients undergoing intravenous and selective studies. A significant rise of LDH or SHBD activity occurred in 4.8 per cent and of CPK in 2.9 per cent of the cases including 1 patient with lymphoma and 1 with gangrene. SGOT and SHBD, on the other hand, showed a significant decrease in activity after the procedure in a higher or equal percentage. Some of the elevations in LDH and SHBD activity may have been due to liver cell injury or undetectable hemolysis.

From the above, CPK seems to be the enzyme of choice for testing minor myocardial cell injury, providing there is no

concomitant skeletal muscle damage. In only 2 of 104 patients having CPK determination or 1.8 per cent was there a suggestion of heart muscle cell injury following angiography. None of the 20 patients undergoing selective coronary arteriography showed changes in enzyme activity above the normal range.

From these studies, it would appear that enzyme activity is not greatly altered by angiography via the intravenous and selective routes. The total incidence (7.1 per cent when 1 patient with lymphoma and 1 with gangrene are excluded) and degree of enzyme elevation found in this study were less than in previously reported series. This may be due in part to the fact that none of the patients had the trauma associated with transseptal catheterization and furthermore, the total duration of our angiographic procedures were less, since they did not include right and left heart catheterization.

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CLINICAL EXPERIENCE WITH A NEW ANGIOGRAPHIC CONTRAST MEDIUM SODIUM/MEGLUCAMINE IOTHALAMATE 78 PER CENT*

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THE ever increasing clinical utilization and application of contrast angiography in the study of a wide variety of disease conditions dictates a continued search for safer and more satisfactory angiographic contrast media. Previous reports from this laboratory have documented the fact that sodium iothalamate 80 per cent (angio-conray) and 1:2 sodium/N-methyl glucamine diatrizoate 90 per cent (hypaque M-90) are the least toxic of the currently available *concentrated* angiographic contrast media.[1,2,5,6] Even so, in experimental animals each of these media produces easily demonstrable neurotoxic and nephrotoxic effects. In a recent experimental study, using standardized toxicity tests, 1:2 sodium/N-methyl glucamine diatrizoate 90 per cent was compared to 1:2 sodium/N-methyl glucamine iothalamate 90 per cent. In equivalent solutions the iothalamate preparation proved to be less toxic than the diatrizoate preparation as regards neurotoxicity, nephrotoxicity and cardiopulmonary toxicity.[4] These results prompted a clinical trial with 1:2 sodium/N-methyl glucamine iothalamate 78 per cent. This medium had the experimental designation MP 3064, and has been named cardio-conray. The 78 per cent solution containing 400 mg. I/ml. was chosen for clinical application because it provides optimum balance between iodine content, viscosity and meglucamine content of the solution. We have used sodium/meglucamine iothalamate 78 per cent to perform 338 angiographic studies in 311 patients. Our experience prompts us to suggest adoption of sodium/meglucamine iothalamate 78 per cent as the contrast medium of choice whenever a concentrated medium is required.

CASE MATERIAL AND METHODS

The 338 angiographic studies were done in 311 patients. They ranged in age from 4 to 77 years, the majority (80 per cent) being in the third to the sixth decade of life. Table I lists the variety of angiographic procedures performed, the number of injections of contrast medium and the dosage range per examination. The vast majority of the procedures employed the Seldinger technique for percutaneous insertion of a No. 6, 7 or 8 French teflon catheter via a femoral or axillary artery into the thoracic or abdominal aorta. Venocavography and right heart angiocardiography were performed by the same technique via a femoral vein. Eight of the abdominal aortographies were done by the translumbar technique. Selective coronary arteriography was done with Sones catheters inserted via an axillary artery. Those procedures listed as thoracic and abdominal aortographies (2 injections) involved first a 60 ml. injection in the ascending thoracic aorta then a 45–60 ml. injection in the upper abdominal aorta. Frequently a third injection was made at the aortic bifurcation to demonstrate the iliac-femoral-popliteal arterial system. Injections into the aorta, vena cava, left or right heart were done with a Cordes pressure injector set at 500–600 pounds per square inch. Selective coronary and visceral arteriography was done by manual injection. Premedication generally consisted of secobarbital, 100 mg., injected intramuscularly 1 hour before the procedure, and meperidine, 100 mg., injected intravenously immediately before insertion of the catheter. In general, selective arteriography involved multiple injections of the contrast medium (2 to 4 injec-

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Table I

VARIETY AND NUMBER OF ANGIOGRAPHIC STUDIES

	No. of Studies	No. of Injections	Dosage Range per Examination
Abdominal aortography	176	190	60–160 ml.
Thoracic aortography	43	51	50–200 ml.
Thoracic and abdominal aortography (2 injections)	20	45	100–225 ml.
Selective coronary arteriography	7	32	14–250 ml.
Coronary arteriography (aortic injection)	16	22	60–150 ml.
Venocavography	19	24	40–180 ml.
Selective angiography	18	31	30–160 ml.
Selective visceral arteriography	37	76	20–180 ml.
Splenoportography	2	2	24–30 ml.
Totals	338	473	

tions) into the selected artery. A single injection of 45–60 ml. of contrast medium was generally the rule in the aortic studies; however, two or more injections of the full dose of medium were performed in 14 of the abdominal aortographies, 8 of the thoracic aortographies and 5 of the combined thoracic and abdominal aortographies. The results of each angiographic procedure were graded as to quality of the study. The patient reaction to the procedure was carefully evaluated. Systemic blood pressure was recorded before and after each procedure. The electrocardiogram was monitored in intracardiac, coronary and aortic root injections. Pre- and serial postangiographic laboratory studies consisting of urinalysis, white blood cell count, hematocrit, hemoglobin, serum transaminases, serum bilirubin and serum creatinine were obtained in the first 60 patients studied.

RESULTS

The roentgenographic quality of the angiographic studies was graded as good to excellent in each case. Generally, there was slightly less density of opacification than is obtained with sodium iothalamate 80 per cent and better opacification than is obtained with 1:1 sodium N-methyl glucamine diatrizoate 69 per cent (renovist), N-methylglucamine diatrizoate 76 per cent (renografin), or 1:2 sodium N-methyl glucamine diatrizoate 90 per cent and 75 per cent (hypaque).

Many of the patients displayed a significant decrease in systemic blood pressure following intravenous administration of 100 mg. of meperidine hydrochloride; however, there were no significant changes in blood pressure following contrast medium injection. The serial hematologic and other laboratory studies performed in 60 patients showed no significant alterations in any patient.

Most of the patients had a transient flushing and warmth following injection of the contrast medium. Pain at the injection site of slight to moderate degree was noted in 38 per cent of the patients; however, this was transient and subsided within a few seconds. Other minor reactions were nausea in 38, emesis in 5, headache in 22, dyspnea in 14 and dizziness in 3. Transient cardiac changes consisting of extrasystoles or bradycardia were noted in 4 patients. Four patients developed hives which responded promptly to intravenous diphenhydramine hydrochloride.

One patient had a complication which may have been related to the contrast medium. A 52 year old woman underwent coronary arteriography by means of an aortic root injection of 60 ml. of the contrast medium. The catheter tip was located in the ascending aorta 2 cm. above the aortic valve. Following the injection she complained of a transient headache. Five minutes later, after the headache had subsided, a second injection of 40 ml. of the contrast medium was made. The headache recurred and lasted 15 minutes. Upon re-

turn to her room she had equal strength in her arms and legs and there were no gross neurologic deficits. Several hours later right sided paresthesias and dysarthria were noted. Neurologic examination indicated partial brain stem thrombosis. The speech defect cleared within 24 hours, but gross incoordination of the right arm and leg persisted. She improved over the next 2 weeks at which time she was discharged from the hospital. At that time neurologic examination revealed persistent clumsy gait, absent position sense of right great toe, a Babinski sign on the left and mild incoordination of the right hand. Electrocardiograms throughout this patient's hospital stay consistently revealed myocardial ischemia, as was true before the arteriographic study. During the 2 days prior to arteriography she required meperidine, 25–50 mg. 3 to 4 times daily for relief of angina. A causal relationship between the arteriographies and this patient's brain stem injury seems unlikely but cannot be excluded. There were no other complications in this series of 338 angiographic procedures which could conceivably be attributed to the contrast medium. Two patients did have thrombotic complications secondary to arterial injury from a catheter.

DISCUSSION

At the present time, contrast angiographic procedures requiring concentrated media are usually done with either the diatrizoate salts (hypaque M-90, hypaque 75 per cent, renovist 69 per cent, renografin 76 per cent) or the iothalamate salts (angio-conray or conray 400). Experimental toxicity studies have clearly shown that in equivalent solutions, the iothalamate salts have less neurotoxicity, less nephrotoxicity and less cardiopulmonary toxicity than the diatrizoate salts.[4] Other recent studies have indicated that the N-methyl glucamine salt media may be safer than sodium salt media, especially in the coronary circulation.[3] These observations led to the present clinical study of a sodium/meglucamine iothalamate which in salt composition resembles hypaque M-90, hypaque 75 per cent and renovist 69 per cent. In equal dosage the iothalamate preparation gave better radiopacification than the diatrizoate sodium /meglucamine media. The most striking feature was the patient reaction following injection. In equivalent dosage sodium /meglucamine iothalamate 78 per cent caused far less pain or patient discomfort than angio-conray or the diatrizoate media. In the thoracic aorta there was virtually no patient discomfort and in the abdominal aorta the pain experienced was far less than with the other contrast media mentioned above.

The one complication encountered did not appear to be related to the contrast medium. During the period from September, 1962 to May, 1966, we encountered neurologic reactions in 12 of some 200 patients undergoing thoracic aortography with concentrated contrast media. In each instance the neurologic reaction became apparent within a few seconds to a few minutes following injection of the medium. For the most part the reaction consisted of a *grand mal* seizure lasting a few seconds up to a minute and without evidence of any neurologic deficit thereafter. In 2 of the patients the seizure was followed by a coma of 12 to 24 hours duration and then by motor neurologic deficits which cleared completely in 3 to 4 days. None of the patients developed neurologic deficit 3 to 4 hours after angiography. In the complication encountered in the present study it is difficult to believe that sufficient contrast medium could enter the vertebral circulation following an aortic root injection to cause brain stem injury. A much more likely explanation, in this patient, would be hypotension secondary to profound myocardial ischemia due to coronary arteriosclerosis. It might be argued that myocardial ischemia might have been the result of the coronary arteriography. Again, if this were so, it should have been apparent in a few minutes rather than a few hours later. Despite a single possible exception, use of 1:2 sodium/N-methyl glucamine iothalamate 78 per cent in 338 examinations has been devoid of significant complication. We believe that it will become the medium of choice for all angiographic

procedures requiring a concentrated contrast medium: thoracic and abdominal aortography, angiocardiography, venocavography, coronary arteriography and selective visceral arteriography. It provides excellent visualization, minimum discomfort, and a wide margin of safety.

SUMMARY

A new formulation of iothalamate salts, 1:2 sodium/N-methyl glucamine iothalamate 78 per cent, has been tested clinically in the performance of 338 angiographies in 311 patients. The results prompt us to believe that this new medium will become the agent of choice for all angiographic procedures requiring a concentrated contrast medium.

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LYMPHOGRAPHY IN CHYLURIA*

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CHYLURIA, the passage of lymphatic fluid in the urine is invariably associated with lymphatic abnormalities. The recently developed diagnostic examination, lymphography, was utilized in patients with this disease process. Lymphographies were performed in two teaching hospitals affiliated with the National Defense Medical Center, Taiwan, the Veterans General Hospital and the 801 Army General Hospital. Fifteen patients with chyluria were examined. The purpose of this report is to describe the roentgenographic findings as seen on the lymphograms, review other case reports and discuss the etiology, pathogenesis, clinical findings and therapy of chyluria.

HISTORICAL NOTES

A disease in which milky urine is excreted has been described by Hippocrates, Galen and Pheophile.[17] Morgani was the first to associate the disease with the abnormalities of the lymphatics. In 1862 Carter[6,7] formulated the theory that chyluria is caused by rupture of a lymphatic varix into the urinary tract. Ackerman[2] in 1863 explained the development of chyluria on the basis of a mechanical obstruction of the lymphatics between the intestines and the thoracic duct. This theory still prevails. In 1868 Wücherer[38] showed the relationship between filariasis and the tropical form of chyluria. In 1872 Lewis[20] demonstrated the embryo of a nematode in a patient with chyluria and called attention to the close relationship between the presence of chyle in the urine and elephantiasis. In 1882 McKenzie,[22] during an autopsy, demonstrated the intimate relationship of lymphatic ectasia and the urinary tract. Manson[21] in 1901 suggested that lymphatico-venous communications may relieve chyluria. In 1913 Bloch[4] observed cystoscopically a stream of chyle arising from a ruptured lymphatic varix within the urinary bladder. Abnormal communications between the urinary tract and the lymph vessels were demonstrated by means of a retrograde pyelogram in 1934 by Abeshouse.[1] In 1963 Servelle *et al.*[34] reported cases in which the lymphatics of patients with chyluria were demonstrated by lymphography. Since that time several additional case reports have appeared in the English literature.[5,8,12,14,15,27,29,33,35]

ETIOLOGY

Chyluria may be associated with a variety of diseases. The tropical form is most commonly associated with Filaria bancrofti. Other parasites such as Eustrongylus gigas, Taenia echinococcus, Taenia nana as well as malaria, ascariasis and bilharziasis have been found in patients with chyluria.[13,24,39] The parasites often occur in areas where filariasis is common so that it is difficult to be certain which of them are responsible for the development of the chyluria. It is not always possible to demonstrate Filaria in the blood or urine. It has been shown that the skin test in filariasis may become negative in patients with known filariasis. Therefore, the absence of larvae in blood or urine does not rule out Filaria as the etiologic agent.[24] The larvae of Filaria bancrofti are transmitted to the human by mosquitoes. It is not known if the larvae gain entrance through the mosquito bite or penetrate the adjacent skin. The parasites have an affinity for the lymphatic system. They migrate into the large lymphatic vessels and nodes where they reach maturity. The living worm usually causes diffuse endolymphangitis with lymphocytic and eosinophilic infiltration

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and fibroblastic proliferation. The more serious damage occurs upon death of the parasite when a granulomatous inflammatory reaction is provoked. The walls of lymphatic vessels swell from edema and eosinophilic infiltration. Central foci of necrosis follow and finally this is replaced by fibrous tissue. When the number of worms is large, lymphatic obstruction may result.

Filariasis occurs in endemic areas. These include the tropical and subtropical countries of Asia, Africa, Australia and America, particularly along the seacoast and the neighboring islands. It is not uncommon in Puerto Rico and most of the case reports in the American literature have originated there.

The nontropical form of chyluria is usually associated with a process which is believed to cause stenosis or obstruction of the thoracic duct. The variety of etiologies associated with this form includes malignancies—especially those which involve the retroperitoneum, chronic inflammatory disease such as tuberculosis, abscesses, trauma, pregnancy, and aneurysm.[13,17,24,32,34,37,39] A case of chyluria developing only during the period of menstruation has also been recorded.[10]

CLINICAL FINDINGS

Since chyluria is only a symptom and not a disease, the clinical findings will depend on the primary cause.

The onset is usually sudden, often associated with trauma or straining.[30] Many patients complain of high back pain and lassitude. Abdominal discomfort is not infrequent. Renal colic may occur if blood clots accompany the chyluria. The presence of blood in the urine is common. The duration of chyluria is rarely more than 2 weeks and in the majority of the cases it lasts less than a week. The attack may cease as dramatically as it started but recurrences are very frequent.

The character of the urine is typical. In chyluria without associated hematuria the urine appears milky. This haziness can be cleared by shaking the urine with ether or chloroform. Another simple test is ingestion of butter colored by Sudan III which in the presence of chyluria will result in a bright orange color of the urine.

TREATMENT

Antifilarial drugs may be used in the endemic areas. The chyluria itself has been treated by lavage of the bladder and/or renal pelvis with silver nitrate solutions. Surgical strippings of renal pedicle lymphatics has also been advocated. The results are difficult to evaluate since spontaneous remissions are common.

It is beyond the scope of this paper to describe the clinical findings and therapy in detail. The interested reader is referred to excellent articles by Yamauchi[39] and Ray and Rao[30] in which these findings are discussed.

ROENTGENOGRAPHIC FINDINGS

The roentgenographic findings in the 17 cases published in the English literature and in our 15 patients are summarized in Table I.

Intravenous urography rarely reveals any abnormality, but reflux and intrarenal extravasation may be seen.[39] In patients who undergo retrograde pyelography, pyelolymphatic backflow is often readily demonstrated. It is of interest that there is little correlation between the retrograde pyelographic findings and the lymphogram in demonstrating the degree of involvement, *i.e.* one may find more advanced changes on one side by retrograde pyelography, while on the lymphographic examination, done at the same time, the other side may appear more severely involved (Table I).

The most striking changes seen on lymphography are the moderate to marked increase in the number and size of the pelvic and retroperitoneal vessels (Fig. 1*A*). These vessels are tortuous and local dilatation may reach several millimeters in

diameter (Fig. 2). Emptying time may be markedly delayed. In contrast to the normal examination in which the vessels empty within a few hours, chyluria patients may take several days to clear their lymphatics of contrast material. When associated with elephantiasis, dermal backflow and large tortuous vessels are seen in the involved extremities. This involvement may be uni- or bilateral. Similar patterns are found in the genitalia (Fig. 3). A significant decrease in the number of visualized lymph nodes is a fairly consistent finding. This is particularly marked in the retroperitoneal area (Fig. 1*B*). In our patients there was a definite correlation between the degree of decreased filling of the lymph nodes and the increase in size, tortuosity, and number of lymph vessels.

The left kidney was more often involved, and when both kidneys were affected it was usually the left one which showed more pronounced changes (Fig. 4). In several instances a "halo" of dilated lymphatic vessels surrounded the minor calyces (Fig. 5; and 6, *A* and *B*). Possibly these are the vessels which discharged chyle into the urinary tract. The contrast medium may remain in these intrarenal vessels for long periods of time. One of our patients retained oil in the kidneys for more than 2 months after lymphography. Contrast medium was noted to be in the urinary bladder in several patients (Fig. 7, *A* and *B*). In these patients oil was also identified in the renal pelvis. We, therefore, feel that the contrast medium reached the bladder via the renal pelvis and ureter. We found no direct lymphatic communication with the bladder.

In none of our patients was the thoracic duct obstructed and we were able to visualize it in most patients (Fig. 8, *A* and *B*). The only abnormalities seen were in 1 patient with retrograde flow to the axilla. This patient had a duct which was widened in its most cranial part (Fig. 9). In another patient, the thoracic duct emptied into the veins through multiple small channels instead of the commonly found single channel.

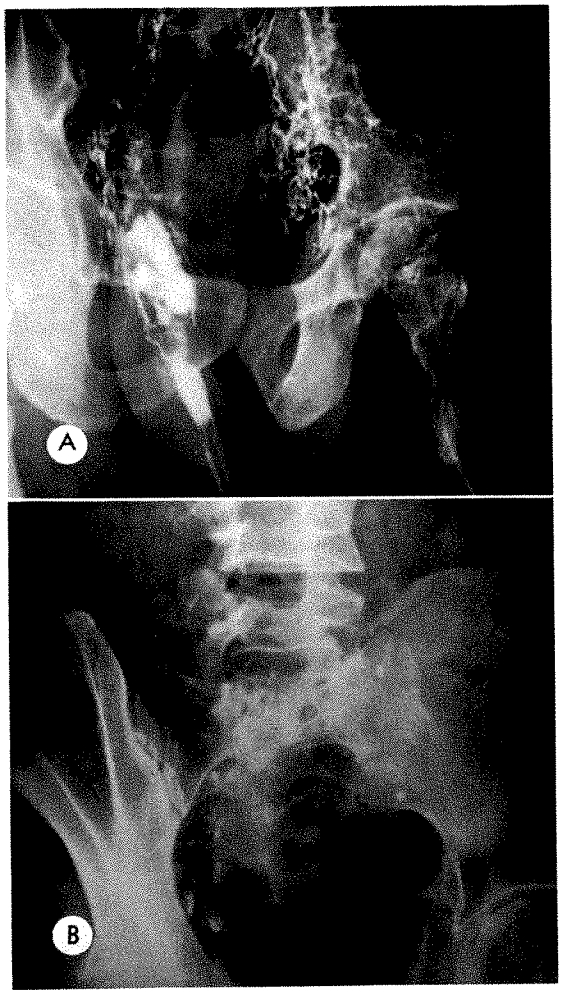

Fig. 1. Case xiv. Roentgenograms of a 40 year old male with a 10 year history of hemochyluria occurring several times yearly. Examination for filariasis was negative. Patient's wife and sons had chyluria. (*A*) Lymphogram demonstrates an increase in number and tortuosity of the pelvic lymph vessels. (*B*) Twenty-four hours following *A*. The vessels are empty. Note the marked decrease in number of pelvic and retroperitoneal lymph nodes. This is a typical and fairly consistent finding in patients with chyluria.

Abnormal thoracic ducts were described by Servelle *et al.*[34] in 3 patients with nontropical chyluria.

Collateral channels to lymph flow are not rare. They are primarily along the

TABLE I

Author	Pelvic and Retroperitoneal Lymph Vessels	Pelvic and Abdominal Lymph Nodes	Lymphatics of the Kidneys	Thoracic Duct	Remarks	Retrograde Pyelography
Kittredge *et al.*[16]	Massive dilatation suggesting anastomosis with bladder	Not demonstrated in retroperitoneum or pelvis	More on left	Seen filled on 96 hour study	Ethiodol found in urine	
Swanson[35] Case I	Slight dilatation and tortuosity	Fewer than normal	More on left than right	Normal (lower)		Reflux on right
Case II	Extensive dilatation and collaterals	Very few lymph nodes	More on left than right; calyces outlined with contrast medium	Somewhat dilated		No definite reflux
Servelle *et al.*[34] (nontropical, post trauma) Case I	Iliac and vulvar vessels are tortuous and enlarged	Not stated	Not stated			
Case II	Increase in number	Not stated	Kidneys equally involved; contrast medium filling right renal pelvis	Blocked at lower third, T9; widened up to that point		
Case III	Some increase in size	Essentially normal	Somewhat more on right than left	Marked tortuosity and dilatation up to T7; anastomosis with intercostal vessels		
Case IV (nontropical infection)	Popliteal and thigh vessels abnormal	Tortuous; increased in size and number; many abnormal vessels in left lumbar area leading to intercostal vessels	Only left filled	Not completely filled; lacy mesh along post-thoracic wall probably due to thoracic duct obstruction		
Case V (nontropical post infection)	Sinusoid in right lower extremity; increased in pelvis	Not stated	Filling only on left	Normal to T4 then conversion into sinusoidal mesh		
Ortiz *et al.*[27] Case I	Distended	Decreased	Very prominent	Filled on roentgenograms; appears normal		Pyelolymphatic reflux on left
Case II	Dilated and increased	Decreased	More on left	Filled on roentgenograms; appears normal		
Kishimoto *et al.*[14]	Distended and slightly increased	Increased	Left involved more than right	Not visualized		Extensive pyelolymphatic reflux on right, less on left
Choi *et al.*[8]	Extensive dilatation still present after 24 hours	Poorly filled	Left slightly more involved	Not seen		Marked pyelolymphatic reflux
Callahan *et al.*[5]	Some increase	Slightly decreased	Right significantly more involved than left			
Ishida *et al.*[12] Case I	Extensive dilatation; increase in number and size	Not stated	Left slightly more involved than right	Patent		
Case II	Extensive dilatation; increase in number and size	Decreased	Right more involved than left; calyces filled with contrast medium	Patent	Ethiodol found in bladder	No reflux
Pomerantz and Jones[29]	Normal	Slightly decreased lymph nodes in left iliac chain	Extensive communication on left	Patent		
Schield *et al.*[33]	Increased number, width and tortuosity; delayed emptying	None seen on 24 hour study	Right significantly more involved than left; filling of calyces on right	Not stated		Pyelolymphatic reflux, more pronounced on left
Koehler *et al.** Case I	Dilatation, tortuosity with "varicosity" appearance from inguinal up to renal region	Markedly decreased; most pronounced in retroperitoneum	Bilateral involvement, more on left	Normal	Contrast medium still seen 26 days after injection on left; contrast medium seen in bladder	
Case II	"Varicosity" appearance with tortuosity and dilatation	Markedly decreased	Bilateral involvement, more on left	Not well demonstrated		

* This communication.

. Table I—(*Continued*)

Author	Pelvic and Retroperitoneal Lymph Vessels	Pelvic and Abdominal Lymph Nodes	Lymphatics of the Kidneys	Thoracic Duct	Remarks	Retrograde Pyelography
Case III	Dilatation, tortuosity (varicose) in periaortic region (L2–L4)	Decreased	Bilateral involvement, more on left	Normal	Contrast medium seen in bladder	
Case IV	Normal appearance of lymphatics and lymph nodes	Slightly decreased, particularly in retroperitoneum	Pericalyceal vessels seen	Normal		
Case V	Tortuosity and dilatation at L1–L3, on the left side	Normal	Bilateral involvement	Minimal tortuosity (normal variant)		
Case VI	Early roentgenogram unavailable	Decreased in retroperitoneum; normal in pelvis	Bilateral involvement, more on left	24 hour study	With intravenous pyelography the contrast medium is seen in vessels surrounding the minor calyces	
Case VII	"Varicosity" appearance in left renal pedicle; increase in size and number	Slightly decreased	Filling only on left	Not well seen		
Case VIII	"Varicosity and pooling" but total number only slightly increased	Decreased	Bilateral involvement	Normal	Filling of vessels in area of genitalia	
Case IX	Marked "varicosity and pooling" of contrast material in renal pedicle	Decreased in periaortic region; fairly normal in pelvis	Bilateral involvement	Normal		
Case X	Marked varicossity; number and size of vessels increased	Decreased in pelvis; almost absent in retroperitoneum	Bilateral involvement, left more than right	Normal	Contrast medium seen in bladder	
Case XI	Tortuous and dilatated lymph vessels in inguinal region and pelvis	Markedly decreased	Bilateral involvement	Normal		
Case XII	Peripelvic communication, with tortuous vessels	Normal	Bilateral involvement	Normal		
Case XIII	Dilatation and pooling in periaortic region, more on left	Decreased	Bilateral involvement, more on left	Normal		
Case XIV	Pelvic and periaortic lymph vessels marked; varicosity	Decreased	Pericalyceal involvement of right kidney	Tortuous and dilated	Tortuous thoracic duct; both supra and infraclavicular and axillary lymphatics on left side are visualized; at 65 day follow-up, contrast medium still present in right kidney	
Case XV	Increased in number and size of vessels; varicosity	Decreased	Bilateral involvement, more on left	Normal		

retroperitoneal vessels and along the intercostal routes. As in all cases of lymphatic obstruction, retrograde flow into dermal or deep pelvic lymphatic plexuses may be found.

DISCUSSION

The classical and most widely accepted theory on the pathogenesis of chyluria, the one quoted in practically every publication on chyluria, was advanced by Ackerman.[2] In 1863, he postulated that chyluria occurs when one or more of the great lymphatic trunks, particularly the thoracic duct, becomes obstructed. He felt that this obstruction necessitates the formation of anastomoses to drain the lymph from the intestine and pelvis. The increased pressure from this lymph flow is then relieved by retrograde flow into the

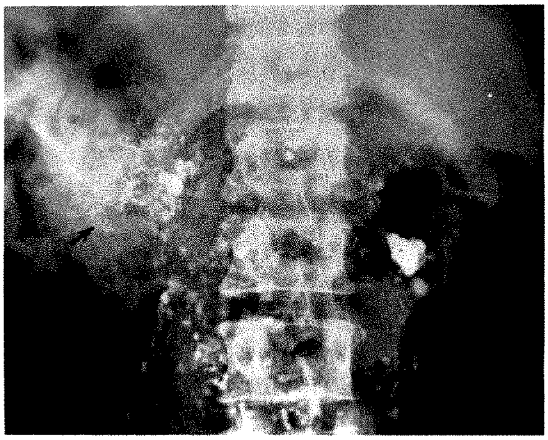

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FIG. 2. Case IX. Lymphogram of a 39 year old male with a history of hemochyluria of 8 years' duration. In 1958 he was treated with antifilarial drugs. The lymphogram shows marked dilatation of the retroperitoneal vessels and the vessels leading to the kidneys, particularly on the right. Intrarenal branches are easily demonstrable. Fine ring-like vessels surround several minor calyces (arrow). This patient was subsequently operated upon and the lymphatics around the pedicle of the kidney were stripped. The chyluric urine cleared following surgery.

lymphatics of the urinary tract. Carter[6,7] postulated that these varicose vessels then rupture and chyluria results.

Lymphography has permitted us for the first time to observe the abnormal morphology and dynamics of the lymphatic system in this disease in living patients. These observations, as well as experimental studies on lymphatic flow following lymph vessel obstruction, cast serious doubts on the validity of Ackerman's and Carter's theories.

In their now classical experiments, Blalock *et al.*[3] studied the consequences of lymphatic obstruction in dogs. They attempted to produce the obstruction by blocking the thoracic duct in the neck and chest and destroying major abdominal lymphatics. It was extremely difficult to completely obliterate all the lymphatics since collaterals, particularly lymphatico-venous anastomoses, quickly developed. Nevertheless, in 3 animals they were able to obstruct completely the lymphatic flow. These animals died and at autopsy a striking picture of markedly distended abdominal lymphatics with extravasation of chyle into many organs was found.

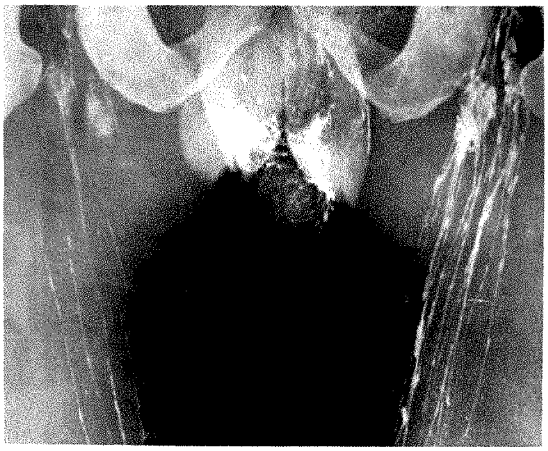


FIG. 3. Case X. Demonstration of lymphatic backflow into the lymph vessels of the penis and scrotum. This 43 year old male had a history of chyluria for 3 months. His chief complaint was passage of milky urine. Intravenous urography was normal. The diagnosis was made and the patient treated for filariasis 7 years prior to lymphography.

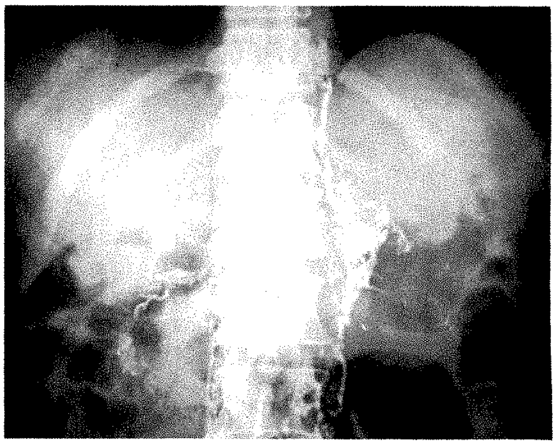


FIG. 4. Case V. Lymphogram of a 42 year old female with history of chyluria for 6 months. This illustration outlines the abnormal lymph vessels penetrating the kidneys bilaterally. It also shows the abdominal portion of the thoracic duct or a major lymphatic trunk leading to the thoracic duct.

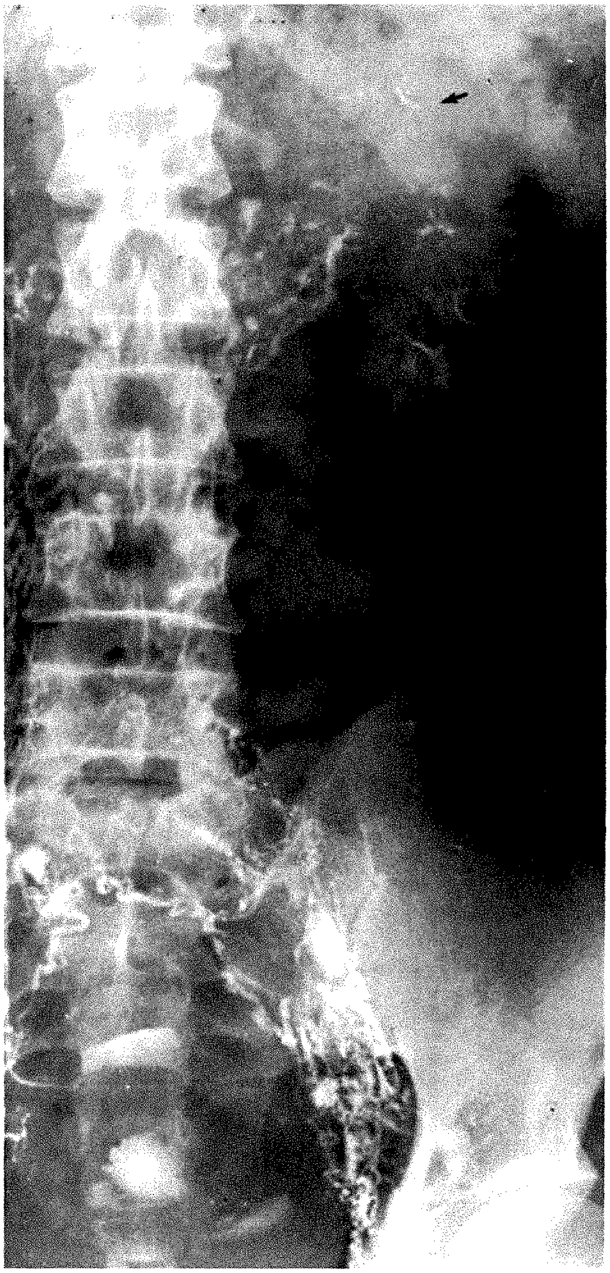


Fig. 5. Case 1. Lymphogram of a 57 year old male with a history of chyluria for 20 years. The diagnosis of filariasis was established in 1947. He has been treated on and off ever since the diagnosis was made. This figure illustrates the tortuosity and increase in number and size of lymph vessels in the pelvis, retroperitoneum and the abnormal connections with the kidneys. Note the fine curvilinear lines which correspond to the minor calyces in the kidney (arrows).

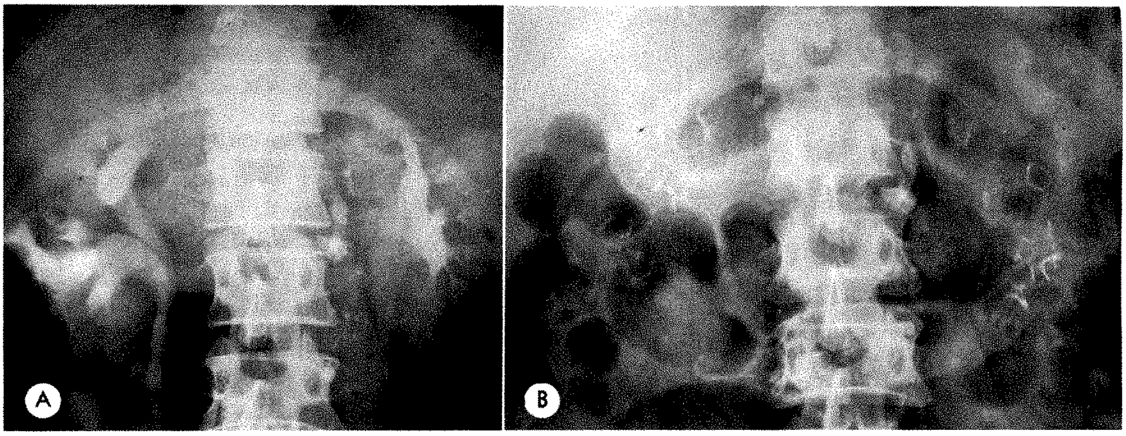
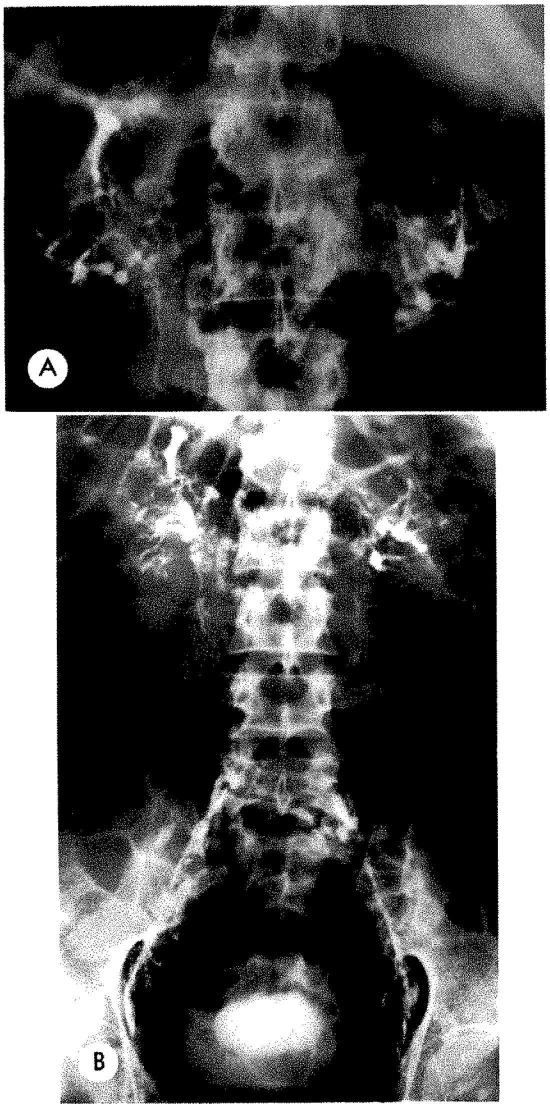


FIG. 6. Case VI. Roentgenograms of a 48 year old female with a history of chyluria lasting 2 years. She has been treated with renal and pelvic lavage with 1 per cent silver nitrate. (*A*) Intravenous urogram showing some fullness of the renal pelvis but essentially normal minor calyces. (*B*) Roentgenogram taken 24 hours following a lymphogram outlining the fine lymphatic vessels which surround the minor calyces.



None of their animals developed chyluria.

Recently, Neyazaki *et al.*[25] and later Takashima and Benninghoff[36] ligated the thoracic duct and then studied lymphatic dynamics by means of lymphography. In their article Takashima and Benninghoff state, "concerning the reflux of Ethiodol, in none of our experimental studies did it occur into the kidneys." Mistilis *et al.*[23] examined a patient with thoracic duct obstruction. Lymphography showed dilatation of intestinal lymphatics, but there was no chyluria.

In our series of 15 patients with chyluria, 13 had completely normal thoracic ducts. Normal thoracic ducts were also reported by most other investigators who examined patients with chyluria by lymphography. We have no answer to the question as to why or how chyluria develops. However,

FIG. 7. Case VIII. Roentgenograms of a 34 year old male with a 15 year history of chyluria. Cystoscopy revealed efflux of milky urine from both kidneys. (*A*) Close up view of the lymphatics of the kidney at the end of injection of ethiodol intralymphatically. Note the abnormal connections of the renal lymphatics. Several of the calyces, particularly on the right, are filled with the oily contrast medium. (*B*) Roentgenogram taken a short while later showing further filling of calyces and pelvis with ethiodol. The ureter (arrows) is outlined. Significant amount of oil can be identified in the urinary bladder.

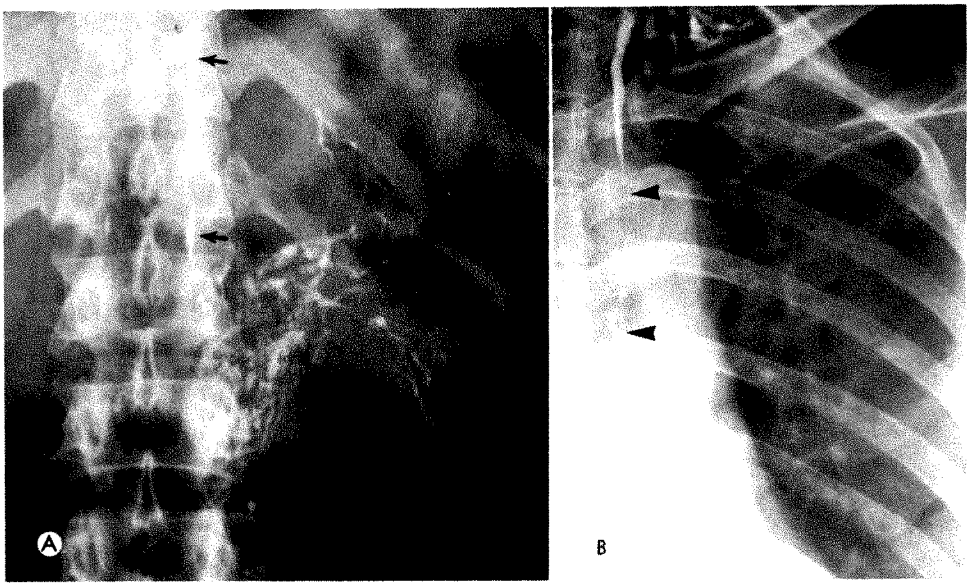


FIG. 8. Case XIII. Roentgenograms of a 41 year old male with a 1 month history of chyluria. (*A*) Lymphogram showing extensive involvement of the lymphatics of the left kidney. There is filling of the abdominal part of the normal thoracic duct (arrows). (*B*) On a chest roentgenogram taken at the same time, the thoracic duct appeared normal in caliber (arrows); however, instead of a single channel entering the venous angle, multiple small channels filled.

the explanation that chyluria is the result of thoracic duct obstruction can no longer be accepted. We would like to speculate that the extensive fibrous replacement of retroperitoneal lymph nodes which results in local obstruction may play a role in the development of chyluria.

The next question which arises is: Is it indeed necessary for a lymphatic vessel to rupture in order to produce chyluria?[6,7] It is not possible to prove that this does not occur, but Lee's[18,19] work on lymphatic permeability suggests that this may not be the case. It is known that fluids and particles may enter and leave intact lymph vessels and that this flow is greatly influenced by the relationship between intralymphatic and interstitial hydrostatic pressures.[31] In chyluria the intralymphatic pressure is greatly increased. It is, therefore, conceivable that the lymph from the distended intrarenal vessels may reach the renal pelvis without previous rupture of the vessels. In 3 patients we demonstrated widened lymph vessels which surrounded the edges of the minor renal

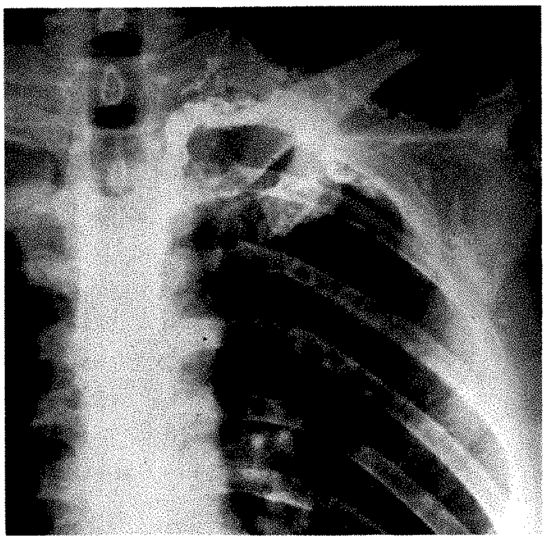


FIG. 9. Case XIV. Roentgenogram of a 42 year old female with a 6 month history of chyluria and soreness in both groins. Physical examination was otherwise unremarkable. A chest roentgenogram taken at the end of intralymphatic injection of ethiodol shows the dilated upper end of the thoracic duct. Collaterals and retrograde filling towards the axilla are noted. The caliber of the thoracic duct up to the level of T4 was normal. This was the only grossly abnormal thoracic duct seen in this series of 15 patients.

calyces (Fig. 5; and 6, *A* and *B*). It is possible that such vessels are responsible for the presence of chyle in the urine.

No experimental model has yet been devised to produce chyluria, and definite answers to these questions must await further investigations. It is hoped that by using lymphography for studies of lymphatic flow *in vivo*, a better understanding into the mechanisms responsible for the development of chyluria will evolve.

SUMMARY

Chyluria is invariably associated with lymphatic abnormalities. As part of our study, 15 patients who manifested chyluria were examined by means of lymphography.

In Table I are summarized the roentgenographic changes found on the lymphograms of these 15 patients and 17 others which were reported in the English literature. There was a moderate to marked increase in number, size and diameter of pelvic and retroperitoneal lymph vessels. The vessels were tortuous. When chyluria was associated with elephantiasis, similar appearing vessels could be found in the swollen extremities and/or genitalia. Many abnormal communications between the retroperitoneal and renal lymph vessels exist. Intrarenally, these vessels follow the collecting system and not infrequently a fine halo of lymph vessels can be seen surrounding the minor calyces. An important, fairly consistent finding was the marked decrease in the number of visualized lymph nodes in the pelvis and retroperitoneum. These lymph nodes fail to visualize because of fibrosis. The fibrotic lymph nodes contribute to the formation of lymph stasis and obstruction.

The thoracic duct was usually visualized. In our series the duct was normal in 13 out of 15 cases. This finding is also confirmed by others.

The roentgenographic demonstration of a normal thoracic duct in patients with chyluria, and experimental studies of lymphatic dynamics following thoracic duct ligation, cast serious doubt on the currently prevailing theory on the pathogenesis of chyluria, in which lymphatic backflow caused by an obstructed thoracic duct is believed to be the cause for the appearance of the lymph in the urine.

The pathogenesis of chyluria in light of new evidence obtained by *in vivo* observation of lymphatic dynamics in chyluria is discussed. The etiology, epidemiology, clinical manifestations and therapy are briefly considered.

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THE CONTRIBUTION OF LYMPHANGIOGRAPHY IN THE STUDY OF DIFFUSE LYMPHANGIOMYOMATOSIS*

REPORT OF A CASE WITH ANATOMIC OBSERVATIONS

By M. COLLARD,† M. FIEVEZ,‡ S. GODART,§ *and* J. P. TOUSSAINT||

IN SPITE of the extension of the indications of lymphangiography, roentgenologic semeiology of the lymphangioma is based solely on meager and recent experience.

In lymphangiomyomatosis, an exceptionally rare pathologic entity, the lymphangiographic aspect has been reported only once before in the literature.[8]

Over a period of 5 years, we were able to study clinically and roentgenologically a case of diffuse lymphangiomyomatosis. In the following we wish to report it and give a description of the anatomic aspect of the entity.

REPORT OF A CASE

H.D., a female born in 1926, presented, in 1961, with a left pleural effusion which absorbed spontaneously.

One year later, the pleural effusion recurred but this time on the right side and could not be controlled despite repeated aspirations. The effusion was accompanied by progressive dyspnea. Examination of the aspirated fluid revealed it to be of a chylous nature.

Lymphangiography was performed in an attempt to locate the origin of the chylous fistula. Resistance to the injection of the contrast medium (ultrafluid lipiodol) was far greater than usually observed, although the macroscopic aspect of the intubated lymphatic vessels was normal. Progression of the liposoluble contrast material was very slow.

Two lymphangiograms made at an interval of 20 minutes, without changing the position of the patient, indirectly demonstrated a lymphovenous communication in the pelvis, on the right side. A progressive accumulation of lipiodol droplets, immiscible with blood, was observed at the level of the right iliac vein valvulae (Fig. 1, *A* and *B*). The lipiodol stopped at the level of the lower lumbar lymph node chain (Fig. 2). This lymphangiographic appearance pointed to the existence of a proximal lymphatic trunk obstacle, probably situated in the thoracic duct, and quite apart from any neoplastic complex.

Following repeated aspirations, pleural synechiae progressively developed; the pleural symptoms diminished and then totally disappeared.

Four months later, a routine roentgenologic examination showed that the lumbar lymphatic block persisted and that the liposoluble contrast medium had flowed back into the mesenteric network, where it had collected into numerous cystic ectases. A slight peritoneal effusion was associated with the lymphatic stasis (Fig. 3).

The evolution of the lymphangiographic aspect implied a diagnosis of lymphatic malformation or intrinsic lymphatic truncal pathology.

In March, 1966, the patient was operated on for a double inguinal hernia (Dr. Rubay); the hernial sacs contained a milky fluid having a chylous appearance.

The patient suddenly died 3 months later with acute edema of the lung, without any pleural component.

At postmortem examination, only the thoracic organs could be removed as a whole. A white and firm thickening of the right pleura was observed, which contained cavities of a cystic nature (Fig. 4).

Histology. The conjunctival wall of the "inguinal cyst" first removed (H.D. 67260) showed a certain number of cavities filled with lymph, surrounded by an endothelium and by

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FIG. 1. (*A* and *B*) In the course of the intralymphatic injection of the contrast medium, one observes a progressive passage of the radiopaque droplets, immiscible with blood, in the right iliac vein where they provisionally embolize at the level of the valvulae.

a smooth muscular, more or less hyperplastic, tissue. Papilliform digitations centrally crossed by an arterial or lymphatic vessel, the axis of which was composed of smooth muscular tissue, and the coating of which was endothelial, projected into the principal cystic cavity (Fig. 5, *A* and *B*). In the autopsy specimens (H.D. 74270), these

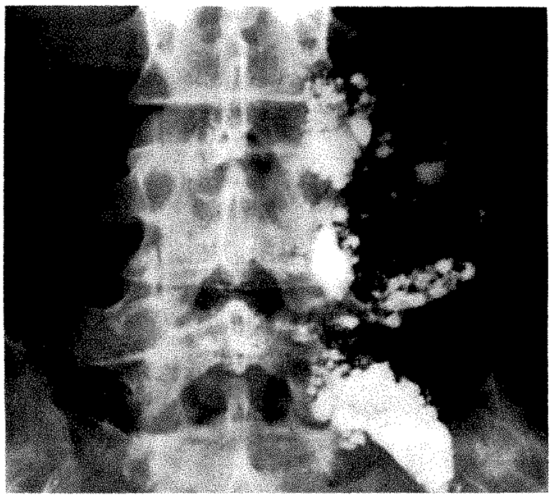

FIG. 2. Six days after the examination, the retroperitoneal progression of the contrast medium is stopped at the level of L3.

FIG. 3. Four months after lymphography, the liposoluble contrast medium has flowed back to the mesenteric network where it is collected into cystic ectases.

Fig. 4. The microroentgenographic study demonstrates the large subpleural cyst-like formations.

same images of angiomuscular proliferation were observed in the thick right pleural adhesions, in various hilar lymph nodes where they had a leiomyomatous appearance, and in a segment of the thoracic duct (Fig. 6, *A* and *B*).

DISCUSSION

The dominant clinical finding of lymphangiomyomatosis, a disease which appears most commonly in female patients about 40 years of age, is chylothorax, sometimes complicated by pericardial or peritoneal chylous effusion.

Our lymphangiographic study constitutes the second roentgenologic report of this disease; to our knowledge, only Deuil *et al.*[8] have carried out lymphography in a case of lymphangiomyomatosis.

The interest of this roentgenologic examination lies in the demonstration of the plurifocal character of the lymphatic affection, while the clinical examination is dominated by the pleural syndrome.

Resistance to the progression of the contrast medium indicates a lymphatic block. Eventual compensation through lymphovenous communications is reflected by a partial venous passage of the lipiodol injected into the lymphatic system.

Several control examinations are necessary to ascertain the route taken by the liposoluble opaque medium; the backflow of the lipiodol into the cystic ectases of the mesenteric lymphatic network suggests that the disease has progressed beyond a purely clinical consideration.

Diffuse lymphangiomyomatosis is usually diagnosed only at postmortem examination. Systematic lymphangiographic examination of the "solitary" lymphangiomas may possibly revise the concept of localization and the "tumorous" nature of the lymphangiomas, and may justify the use of the term "cystic lymphangiectases," which was suggested in 1950 by Delarue *et al.*[7] who gave the first description of the entity.

The lymphangiectases in our case, which showed a characteristic muscular hyperplasia, differ from the usual lymphangiectases only by their particular evolutive relationship to the injured trunks and the length of the period of evolution indis-

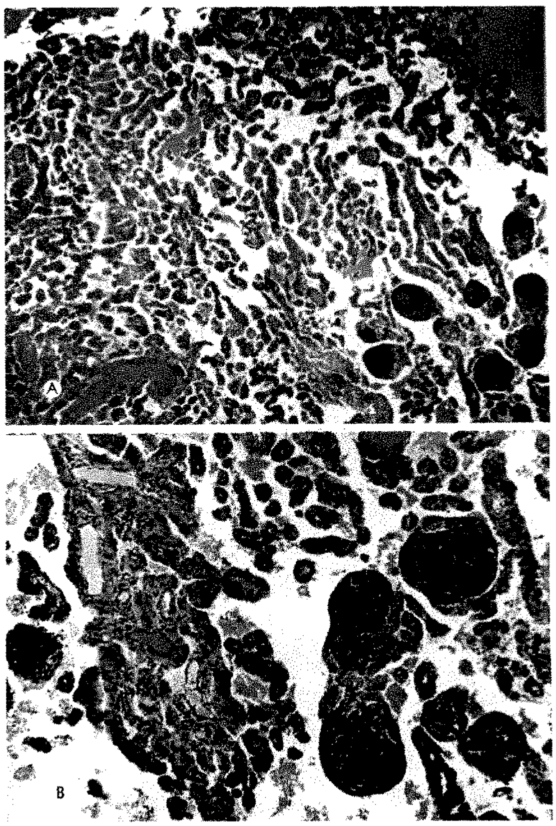

Fig. 5. (*A* and *B*) Low magnification photomicrograph of the inguinal cyst. There is generalized angiomuscular papilliform proliferation, with lymphoid nodules.

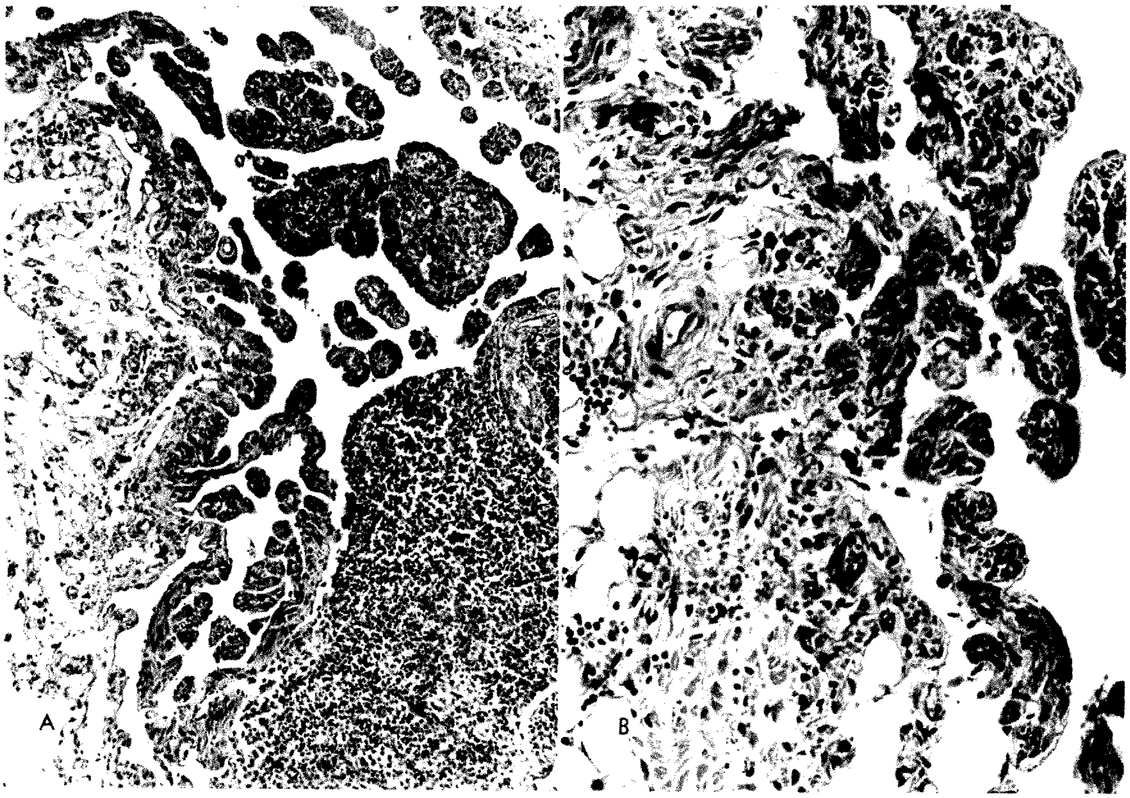

FIG. 6. (*A*) Partial view of the thoracic duct demonstrating the same histologic pattern as in Figure 5. (*B*) Identical angiomuscular proliferation, without lymphoid nodules, in the bands of pleural adhesions.

pensable to the individualization of the lesion.

Malformation of the thoracic duct might be responsible for the lymphatic decompensation and for the chylous thoracic syndrome.

CONCLUSION

Lymphangiography is one of the most important procedures in the study of lymphangiomyomatosis.

This roentgenologic examination may show the diffuse character of the affection, which is clinically dominated by the chylothoracic syndrome.

Systematic use of lymphangiography in localized lymphangiomas is likely to modify the unifocal and tumorous concept of these lesions.

SUMMARY

The clinical evolution and the lymphangiographic findings of a case of lymphangiomyomatosis are described.

Emphasis is placed on the fact that lymphangiography permits establishment of the diffuse character of the lesion, which is dominated clinically by the chylothoracic syndrome.

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THE AMERICAN JOURNAL OF ROENTGENOLOGY RADIUM THERAPY AND NUCLEAR MEDICINE

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EDITORIAL

ACKNOWLEDGMENTS

VENOUS angiocardiography appeared as a practical procedure less than 30 years ago. It added a new dimension to the radiography of the cardiovascular system in that it offered the possibility of the demonstration of any vascular structure that could be made to form an interface with the contrast substance. Initially, only the cardiac chambers and great vessels were reliably demonstrated. Smaller structures, such as subvalvular bands and ridges, the crista supraventricularis and the coronary arteries, were not recognized or were invisible. Also, those elements that undergo rapid motion, such as the valve rings and leaflets, were only occasionally and incompletely seen. The wealth of anatomic detail now provided by angiocardiography in all of its selective applications has occurred through step-wise progress in diverse areas and in a relatively short period of time. Each advance at the time did not seem too impressive, but when the total is reviewed, even from a very short perspective, it is remarkable. This progress has occurred in two general areas of perhaps equal importance, namely technique and interpretation.

Because of the efforts of a relatively few pioneers, it is now possible to place almost any type of catheter in the heart or vascular system via a percutaneous approach. This brought to the radiologist and his nonsurgical colleagues such technical independence and economy of action that they could begin to apply their *own* ideas and concepts to the entire problem of catheter placement. The handicaps of dual responsibility and catheter manipulation by proxy were largely eliminated. Many cardiovascular radiologists have added the technique of arteriotomy to their repertoire, but it is only occasionally needed or used.

Contrast substances are now more innocuous and less viscous than they were 10 years ago, and for this we may thank the commercial drug houses. We *are* waiting for more ideal substances. I submit that of even greater importance is our increased knowledge of how, when and where to use the available substances. This has come from extensive clinical experiences and more basic research regarding osmolarity and protein binding properties. I am happy to note that a few radiologists are engaged in this latter activity and that the picture in this area is still unfolding.

Due to the efforts of a few radiologists and the supporting commercial manufacturers, we have a large and sometimes bewildering array of injection devices. In recent years these have tended towards automatic operation, increased maneuverability and reliability. Again, I submit that the significant advance has been due to our increasing knowledge of how to use our own particular injection system. This has usually come from experience, but it is now reinforced by basic knowledge of the effects of catheter size, diameter, length, pressure and the viscosity of contrast agents on flow rates. Furthermore, we now know how much contrast substance is needed in a given time period and whether our apparatus will provide it. In this same area we are indebted to a number of radiologists and also the commercial houses for the large array of catheter materials, adapters, guide wires, manifolds and other useful accessories that have become increasingly available.

Steady progress in selective catheter insertion was occurring before image ampli-

fication was widely available, but it was limited to the hardier and more persistent workers. Single procedures often required hours of concentrated effort, technical perfection and an abundance of radiation. The image amplifier with television readout immediately changed the hitherto complicated one-a-day procedures into the relatively simple three or more a day variety. To the experienced operator the hitherto dark corners of the cardiovascular system, such as intercostal, internal mammary and coronary arteries, became accessible. Even the timid and less experienced operators were tempted to try their hands at catheter placement and with varying but usually much improved and successful results.

Concurrent with the use of image amplification for catheter placement was the increased availability of cineangiography. Cine recording techniques had for a number of years given great promise of extending the range of angiocardiographic observations. Prior to image amplification the apparatus was cumbersome and the amount of radiation totally unacceptable for general use. Although the radiation problem is still with us to some extent, the image amplifier has made cine techniques as accessible as spot filming, and the problems of angiographic filming have been simplified. Opinion varies as to the superiority of movies over large films, but this is hardly the point. It is a good and readily available substitute. It often complements the large film studies, and in some areas, such as the study of valve structures, it may be the method of choice.

Other fascinating and promising devices, such as tape recorders, kinematic recording systems and 70 and 90 mm. rapid spot film devices, have naturally followed the image amplifier, and their value although unquestioned is yet to be assessed. For these epochal technical developments, we acknowledge with thanks the pioneering efforts of a very small number of radiologists and their supporting group of physicists and engineers.

As physicians we have admired and applauded the monumental advances in the surgical treatment of cardiovascular disease. These have created new challenges for us and have vastly increased our opportunities to learn and develop our specialty. Along with our cardiologic colleagues we feel that we have contributed something in this area and have been glad to have played a part in supporting these great surgical attainments. In a slightly different vein we acknowledge that our surgical and cardiologic colleagues have been the gadflies that have goaded us out of some of our encrusted complacency. In all too many instances they have hastened to do the things that we should have done and with varying success upon which I will not comment further. Where the relationship has developed properly, our colleagues in surgery and cardiology have been a stimulating and constructive influence in initiating our programs, in sending us patients, and in giving their thoughtful advice and counsel in every area. Also, what a tower of strength they can be at the time of a major complication. We acknowledge their contributions with thanks.

Twenty years ago the medical literature and the standard works on anatomy and pathology were relatively sterile in their descriptions of the dynamic structures seen at selective angiocardiography. A newer living radiographic anatomy was needed. Radiologists have been in the forefront of this activity, but let us acknowledge again the contributions of the cardiac surgeons. They have graciously called us to the operating table for a good look and with a minimum of embarrassment. Critical dynamic and anatomic observations available only at the operating table have been fed back to us with liberality. Also, they have borne the pain of providing us with many of our most useful postmortem specimens. Only a few pathologists have concerned themselves extensively in the area of cardiovascular anatomy, but their contributions have been enormous. To appreciate these we need

only to turn through the atlases and numerous contemporary articles and dwell on the magnificent reproductions, line drawings and diagrams and other correlative material. Here is practical anatomy at its best, and we as radiologists are grateful.

It would be naïve to believe that the advances cited above could have combined spontaneously to produce present day selective angiocardiography. All of these elements needed integration, and this has created a new role for the radiologist. It might be argued that the cardiovascular radiologist is not unique but simply a throwback to the earliest period of our specialty. Then the radiologist assumed the complete responsibility of a consultant, namely a mastery of the technical details of his examination and a medical opinion in keeping with the total problems of the patient. This is the role of the cardiovascular radiologist today. He assumes responsibility for the selection of patients, the conduct of the radiologic procedure, the interpretation of the information gained thereby, and recommendations as to further diagnostic and therapeutic procedures. He is ready to deal with and assume responsibility for the treatment of complications and to call for consultation where this is needed. He is familiar with the functions and capabilities of his complex equipment and usually is the only one who really understands its frailties and deficiencies. He has organized his supporting personnel, the instrument nurse, the radiographic and electronic technicians and his professional assistants. He is the director of a small group, each member of which is highly proficient and coordinated for performance as a unit. It is this type of professional support that has been the dominant factor in bringing selective angiocardiography to its present status and satisfactory state of development.

As we assess our progress we must recognize that human initiative, discipline and imagination were indispensable in welding together the diverse knowledge and disciplines necessary to produce satisfactory selective angiocardiography. And so it is likely to be in the future. New devices and instruments will come rapidly, but their proper utilization will require from the radiologist and our colleagues the same human and professional qualities that have already been amply displayed in the development of selective angiocardiography.

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NEWS ITEMS

NEW OFFICERS OF THE RADIOLOGICAL SOCIETY OF NORTH AMERICA

At the Fifty-third Annual Meeting of the Radiological Society of North America held November 27–December 1, 1967 at the Palmer House in Chicago, Illinois, the following officers were elected: *President*—Stanley M. Wyman, M.D., Belmont, Massachusetts; *President-Elect*—John H. Gilmore, M.D., Oak Park, Illinois; *First Vice-President*—Milton Elkin, M.D., New York, New York; *Second Vice-President*—William H. Neil, M.D., Fort Worth, Texas; *Third Vice-President*—Robert Robbins, M.D., Philadelphia, Pennsylvania; *Secretary*—Maurice D. Frazer, M.D., Lincoln, Nebraska; *Treasurer*—R. Brian Holmes, M.D., Toronto, Ontario, Canada; and *Historian*—Howard P. Doub, M.D., Detroit, Michigan.

The Chairman of the Board of Directors is John R. Hodgson, M.D., Rochester, Minnesota.

The Gold Medal of the Society was awarded to John A. Evans, M.D., New York, New York.

The Fifty-fourth Annual Meeting of the Society will be held at the Palmer House in Chicago, Illinois, December 1–6, 1968.

AMERICAN SOCIETY OF THERAPEUTIC RADIOLOGISTS

Election of New Officers

The following officers were elected at the Annual Meeting of the Society of Therapeutic Radiologists in Chicago, November 27, 1967: Gilbert E. Fletcher, M.D., Houston, *President;* Henry Kaplan, M.D., Palo Alto, *Chairman of the Board;* Morton Kligerman, M.D., New Haven, *President-Elect;* and Frank Hendrikson, M.D., Chicago, *Member of the Board.*

The following were re-elected: Simon Kramer, M.D., Philadelphia, *Member of the Board;* Howard Latourette, M.D., Iowa City, *Treasurer;* and J. A. del Regato, M.D., Penrose Cancer Hospital, Colorado Springs, Colorado 80907, *Secretary.*

SPECIAL RADIATION PROCEDURES IN THE TREATMENT OF CANCER

A course of "Special Radiation Procedures in the Treatment of Cancer" will be held Monday, May 27, 1968 through Wednesday, May 29, 1968, 9 A.M.–5 P.M. at the Long Island Jewish Hospital/Queens Hospital Center Affiliation, Jamaica, New York.

There also will be a "Radium Day" on Wednesday, May 29, 1968, 9 A.M.–5 P.M.

For further information and registration forms kindly contact J. J. Smulewicz, M.D., Director, Department of Radiology, The Long Island Jewish Hospital/Queens Hospital Center Affiliation, 82-68 164th Street, Jamaica, New York 11432.

SECOND INTERNATIONAL CONGRESS OF LYMPHOLOGY

The Second International Congress of Lymphology, co-sponsored by the University of Miami School of Medicine, Miami, Florida, will be held March 15–20, 1968, at the Fontainebleau Hotel, Miami Beach, Florida.

This Congress is designed to gather lymphologists from all parts of the world who will present their work and exchange ideas with scientists from many countries. One hundred and sixty-two speakers will represent 24 countries.

The program, due to the large number of scientific papers suggested, will be divided into simultaneous sessions to be held morning and afternoon Saturday, March 16; Monday, March 18; and Tuesday, March 19. There will be morning sessions only on Sunday, March 17 and Wednesday, March 20.

The proposed Symposia will deal with Anatomy, Lymphatico-Venous Anastomoses, Lymphangiopathies, Diagnostic

Procedures, Contrast Media, Lymphography, Endolymphatic Therapy, and Malignant Lymphoma.

Free Communications will deal with Experimental Anatomy and Pathology, Physiology, Liver and Intestinal Lymphatics, Immunology and Transplanation, Kidney Lymphatics, Head and Neck Lymphatics, and Experimental Research.

All of the scientific papers will be presented and discussed in English.

The President of the Congress is M. Viamonte, Jr., M.D., Professor of Radiology, University of Miami School of Medicine, Miami, Florida.

The President of the International Society of Lymphology is A. Ruttimann, PD., Dr., Röntgendiagnostisches Zentralinstitut der Universität, Kantonsspital, Zürich, Switzerland.

For further information and registration forms please address, Office of Postgraduate Medical Education, P. O. Box 875, Biscayne Annex, Miami, Florida 33152.

Hotel reservations will be accepted and confirmed by mail until March 1, 1968. All reservations must be made directly to Mrs. Shirlee Ostroff, Convention Reservation Department, Fontainebleau Hotel, Miami Beach, Florida.

FIRST SOUTH AFRICAN CONGRESS OF RADIOLOGY

The First South African Congress of Radiology will be held in Johannesburg over the long weekend of August 31–September 2, 1968.

Those wishing to participate in the program should submit the title of the proposed paper and the request for the accommodations desired as early as possible.

For further information please write to Dr. Paul Sneider, Organizing Secretary, P.O. Box 4878, Johannesburg, South Africa.

EUROPEAN ASSOCIATION OF RADIOLOGY

Symposium Ossium

A symposium of the diagnosis and treatment of diseases of the bone will be held April 4–6, 1968, in the halls of the Royal Geographic Society and the Department of Mechanical Engineering of the Imperial College of Science and Technology (University of London), South Kensington, London, England.

The proposed topics for discussion are: Radiologic methods in the diagnosis of bone and joint disease; pediatric bone disease; metabolic bone disease; endocrine bone disease; measurement of bone mineral *in vivo;* computers in the diagnosis of bone disease; hemoglobinopathies; arteriography in bone disease; microradiography in bone disease; assessment of result in radiotherapy of osteosarcoma and chondrosarcoma; the radiotherapy of giant cell tumors, Ewing's tumor, reticulum cell sarcoma and malignant synovioma; the place of radioisotopes in the management of joint disease; radioisotope methods for detection of metaphysical technique, comparison of radiodiagnostic stases in bone, choice of radioactive material and isotope methods; physical problems of radiation dosimetry involving bone marrow, cellular radiobiology and relation to radiotherapy technique; induction of bone tumors by radiation, including effects of radioactive materials (strontium, radium, transuranic and other elements); tracer studies of bone metabolism; and ultra-sound (penetration of bone, therapeutic applications).

There will be simultaneous translations into English, French, German and Spanish.

The President of the Association is Professor B. Rajewski, Frankfurt, Germany, and the Secretary General is Professor Ch. Gros, Strasbourg, France.

For further information please write to Dr. J. S. Macdonald, Secretary General Symposium Ossium, 156 Lambeth Road, London, S.E.1, England.

BRITISH COMMITTEE ON RADIATION UNITS AND MEASUREMENTS (BCRU)

The British X-ray Units Committee, which was set up in 1925 with Sir William Bragg as Chairman and was subsequently

changed to the British Committee on Radiological Units, has recently been reconstituted under the chairmanship of Professor F. W. Spiers, C.B.E., as the British Committee on Radiation Units and Measurements (BCRU).

The Committee is now sponsored by the Radioactive Substances Advisory Committee (RSAC), and is based at the National Physical Laboratory.

The functions of the Committee comprise: Acting in an advisory capacity to Government Departments and other bodies through the RSAC on matters concerning radiation units and measurements; interpreting the recommendations of the International Committee on Radiological Units (ICRU) for national use and, when appropriate, formulating proposals for submission to the ICRU and other bodies; and setting up forums and working parties for specific purposes.

The following are the members of the BCRU: T. E. Burlin, P. J. Campion, E. Collinson, F. Ellis, J. F. Fowler, J. R. Greening, W. G. Marley, W. V. Mayneord, G. J. Neary, E. E. Smith, R. C. Tudway and B. M. Wheatley.

The Secretary is Dr. W. A. Jennings, Division of Radiation Science at the National Physical Laboratory, Teddington, Middlesex, England.

BOOK REVIEWS

Books sent for review are acknowledged under: Books Received. This must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interest of our readers as space permits.

HYSTEROSALPINGOGRAPHY. By Alvin M. Siegler, M.D., D.Sc., Clinical Associate Professor in Obstetrics and Gynecology, State University of New York, Downstate Medical Center; Attending Physician in Obstetrics and Gynecology, Kings County Hospital Center and the Brookdale Hospital Center; Director of the Sterility Clinic, Kings County Hospital Center, Brooklyn, N. Y. Cloth. Pp. 418, with 543 illustrations. Price, $21.00. Hoeber Medical Division, Harper & Row, Publishers, 49 East 33rd Street, New York, N. Y. 10016, 1967.

Hysterosalpingography remains the mainstay of roentgen investigation of the female genital tract. Dr. Siegler's book is a review of this subject based on his extensive experience.

The subject material is divided into two sections. The first includes a brief history of the technique, indications and advantages, dangers and methods of examination. The second section relates to interpretation of the hysterosalpingogram and includes a discussion of physiologic variation, congenital anomalies, adhesions, fistulae, tubal patency, inflammatory lesions, and the role of hysterosalpingography in abnormal uterine bleeding and in pregnancy.

The section of the book concerning the author's technique deserves some critical comment. Although new developments in radiographic equipment and technique are mentioned, one gains the impression that Dr. Siegler's examinations are done, for the most part, without benefit of fluoroscopic observation or spot filming. In addition, his technique calls for blind injection of iodized oil without fluoroscopic observation. He reiterates his concern for minimizing radiation exposure of the patient, but uses conventional filming to control filling, waiting for development of each film before proceeding to inject the next increment of contrast material. In the opinion of this review, controlled injection by image intensification fluoroscopy and spot filming is a more accurate, convenient and safer technique, which permits modification to suit the particular circumstances, and which is less expensive in radiation dosage and physician time. The author also prefers the routine use of oily contrast media to the newer water soluble agents.

Except for the technical aspects of this work, the book is an excellent review of the application of hysterosalpingography to clinical medicine. The entities are discussed quite completely and are amply illustrated by roentgenograms of good quality. The text is easy to read and well documented by an ample bibliography.

This book will serve as a useful clinical reference work for the experienced physician but is not recommended as an introductory text for it does not provide the neophyte with an approach to the examination which takes advantage of the rather remarkable improvements in roentgen technique which have taken place in the past 10 to 15 years. The author indicates that hysterosalpingography should be a joint effort of the gynecologist and the radiologist, but this philosophy is not developed in the theme of this book.

THEODORE E. KEATS, M.D.

PATHOLOGY. Third edition. By Stanley L. Robbins, M.D., Professor and Chairman, Department of Pathology, Boston University School of Medicine; Director of the Mallory Institute of Pathology of the Boston City Hospital, Boston, Massachusetts; and Lecturer, Harvard Medical School and Tufts University School of Medicine. Cloth. Pp. 1434, with many illustrations. Price, $20.50. W. B. Saunders Company, West Washington Square, Philadelphia, Pa., 1967.

The Third Edition of this excellent textbook of *Pathology* has been considerably enlarged from the previous edition and many chapters, particularly in the first part, have been thoroughly revised. In spite of increased text, the format of the book has remained as a single volume, but several chapters in the first part have been fused and two new ones dealing with genetics and diseases of aging introduced.

The number of photographs has also been increased and in line with the new develop-

ments and knowledge gained by electron microscopy many of the additional photographs show ultrastructural cellular changes. As in previous editions, the emphasis on correlation of clinical findings with pathogenesis of disease is an outstanding feature of this book. Detailed description of lesions and encyclopedic coverage of all pathologic processes was not attempted before and this policy remains unchanged in this edition. The bibliography is quite sufficient and includes most important and original contributions with new references to recent publications.

All in all, the book is well written and easy to read, contains many passages in bold print and has excellent illustrations. Fine print, which is usually bothersome in most specialty books, is conspicuously absent and this feature makes this book even more attractive.

This textbook is probably most useful for a medical student to introduce him to general problems of pathology and to give him an understanding of disease processes, but can also serve as a quick reference for a practicing physician.

N. Rachmaninoff, M.D.

BOOKS RECEIVED

Palliative Care of Cancer Patient. By 33 Authors. Edited by Robert C. Hickey, M.D., F.A.C.S., Professor and Chairman, Department of Surgery, University of Wisconsin Medical School, Madison, Wisc. Cloth. Pp. 640, with 147 illustrations. Price, $23.50. Little, Brown and Company, 34 Beacon Street, Boston, Mass. 02106, 1967.

Tritium-Labeled Molecules in Biology and Medicine. By Ludwig E. Feinendegen, Services de Biologie, Euratom, Brussels, Belgium; presently at Kernforschungsanlage Jülich, Germany. Prepared under the direction of the American Institute of Biological Sciences for the Division of Technical Information, United States Atomic Energy Commission. Cloth. Pp. 430, with some figures. Price, $17.00. Academic Press Inc., Publishers, 111 Fifth Avenue, New York, N. Y. 10003, 1967.

Fatigue Fractures: A Clinical Study. By James M. Morris, M.D., Assistant Professor of Orthopaedic Surgery; Research Associate, Biomechanics Laboratory, University of California School of Medicine, San Francisco, Calif.; and Loren D. Blickenstaff, M.D., Major, U. S. Army Medical Corps. Cloth. Pp. 218, with many illustrations. Price, $15.50. Charles C Thomas, Publisher, 301–327 East Lawrence Avenue, Springfield, Ill. 62703, 1967.

Cancer of the Head and Neck. By William S. MacComb, M.D., Chief, Section of Head and Neck Surgery; and Gilbert H. Fletcher, M.D., Head, Department of Radiotherapy, The University of Texas M. D. Anderson Hospital and Tumor Institute, Houston, Texas. Cloth. Pp. 598, with many illustrations. Price, $28.50. The Williams & Wilkins Company, 428 E. Preston Street, Baltimore, Md. 21202, 1967.

Roentgen Television: Technical Bases and Clinico-Roentgenologic Application. By Prof. Dr. Alfred Gebauer, Head of the X-ray Department of the Medical Clinics of Frankfurt University, Frankfurt, Germany; Prof. Dr. Josef Lissner, Head Physician of the Clinic for Radiotherapy and Nuclear Medicine of Frankfurt University, Frankfurt, Germany; and Dipl.-Ing. Ottfried Schott, Head of the Basic Research Laboratory of the X-ray Development Department and Scientific Adviser, Siemens Aktiengesellschaft, Medical Division, Erlangen, Germany. Translated by Dr. H. Pucher, Erlangen; and Mr. G. Wall, London. Paper. Pp. 154, with many illustrations. Price, $7.75. Grune & Stratton, Inc., 381 Park Avenue South, New York, N. Y. 10016, 1967.

Familiäre Huftdysplasie bei Huftluxation: Eine Biometrische Untersuchung. By Priv.-Doz. Dr. Detlef v. Torklus, Hamburg. Paper. Pp. 90, with some illustrations and tables. Price, DM 26.-. Georg Thieme Verlag, Stuttgart. In the U.S.A. and Canada, Intercontinental Medical Book Corporation, New York, N. Y. 10016, 1967.

Annual Review of Nuclear Science. Edited by Emilio Segrè, University of California, Berkeley; Associate Editors, Gerhart Friedlander, Brookhaven National Laboratory; and H. Pierre Noyes, Stanford University. Volume 17. Cloth. Pp. 546, with some illustrations. Price, $8.50. Annual Reviews, Inc., 4139 El Camino Way, Palo Alto, Calif. 94306, 1967.

The Radiologic Clinics of North America. Symposium of The Radiology of Ischemia. Guest Editor, Roy R. Greening, M.D. December, 1967, Volume V, No. 3. Pp. 225, with many illustrations. W. B. Saunders Company, West Washington Square, Philadelphia, Pa. 19105, 1967.

PRIME: An Automated Information System for Hospital and Biomedical Research Laboratories. By Lee B. Lusted, M.D., Professor of Radiology, University of Oregon Medical School; Senior Scientist, Oregon Regional Primate Research Center; and Robert W. Coffin, B.A., Chief Programmer, Oregon Regional Primate Research Center. Paper. Pp. 233, with many tables and charts. Price, $7.50. Year Book Medical Publishers, Inc., 35 East Wacker Drive, Chicago, Ill. 60601, 1967.

Scientific Publications from the Eastman

KODAK LABORATORIES. Section I, 1965–1966: Organic Chemistry, Polymer Chemistry, Biological Chemistry. Pp. 110, with many figures. Section II, 1965–1966: Analytical Chemistry, Physical Chemistry, Chemical Engineering. Pp. 95, with many figures. Section III, 1965–1966: Physics, Mathematics, Engineering. Pp. 67, with many figures. Section IV, 1965–1966: Photographic Science and Technology. Pp. 86, with many figures. Published by Department of Information Services, Research Laboratories, Eastman Kodak Company, Rochester, N. Y. 14650, 1967.

ROENTGENOLOGY OF THE SPLEEN AND PANCREAS. By Josef Rösch, M.D., Doctor of Medical Sciences, Docent of the Medical Faculty of Charles University; Roentgenologist of Central Hospital, Prague, Czechoslovakia; Research Fellow, Radiology Department, University of Oregon Medical School, Portland, Oregon. Cloth. Pp. 336, with many illustrations. Price, $29.75. Charles C Thomas, Publisher, 301–327 East Lawrence Avenue, Springfield, Ill. 62703, 1967.

PROGRESS IN EXPERIMENTAL TUMOR RESEARCH. Edited by F. Homburger, Cambridge, Mass. Volume 9. Cloth. Pp. 431, with 85 figures. Price, $15.40. S. Karger Ag. Basel. In the U.S.A., Albert J. Phiebig, P.O. Box 352, White Plains, N. Y. 10602, 1967.

ABSTRACTS OF RADIOLOGICAL LITERATURE

INDEX TO ABSTRACTS

ROENTGEN DIAGNOSIS

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Gynecology and Obstetrics

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Nervous System

RADIATION THERAPY

MISCELLANEOUS

ROENTGEN DIAGNOSIS

Head

Davies, E. R., and Sutton, David. Pseudo-occlusion of the internal carotid artery in raised intracranial pressure. *Clin. Radiol.*, July, 1967, *18*, 245–252. (From: Departments of Radiology, St. Mary's Hospital, London W. 2., and Maida Vale Hospital, London W. 9., England.)

Pseudo-occlusion has been reported in the carotid artery in 25 cases, and in the basilar artery in 1 case. The most frequent underlying cause was intracranial hemorrhage. Primary neoplasm, abscess and trauma have also been described in etiology. The clinical feature common to all these cases was acutely raised intracranial pressure.

The authors have seen 5 cases of pseudo-occlusion of the internal carotid artery due to raised intracranial pressure. The essential feature is that the intracranial pressure is so high that the cerebral circulation is slowed to a marked degree. When such is present contrast material injected into the carotid artery will separate into a dense layer.

The roentgenographic appearances of pseudo-occlusion can be explained in terms of the hemodynamic effect of injecting contrast material into a circulation which has been greatly slowed by rising intracranial pressure.

The immediate prognosis is always poor. The patients are usually very seriously ill when roentgenography is instituted. Arteriography itself may be directly responsible for death of the patient during or immediately after the procedure because the pooling of contrast material in the carotid syphon can completely obstruct the flow of blood. Nearly all the reported cases have died within a few days after hospital admission. However, the condition is potentially reversible in an occasional patient, such as in an operable meningioma partly supplied from the external carotid artery.—*Samuel G. Henderson, M.D.*

Neck and Chest

Siegel, Richard S., and Steichen, Felicien M. Cervicothoracic outlet syndrome; vascular compression caused by congenital abnormality of thoracic ribs: a case report. *J. Bone & Joint Surg.*, Sept., 1967, *49A*, 1187–1192. (Address: Dr. Richard S. Siegel, 2100 Eastchester Road, Bronx, N. Y. 10461.)

The term thoracic outlet syndrome is used to cover all lesions that reduce the cervicothoracic outlet and cause symptoms due to nerve, artery or vein compression. It includes scalenus anterior, cervical rib, costoclavicular, hyperabduction, subcoracoid, pectoralis minor and first thoracic rib syndromes. Since anomalous first ribs usually end at the level of the scalene tubercle posterior to the point where the subclavian vein crosses the first rib, venous obstruction has not been previously reported. The few cases with this anomaly which have been reported have had either arterial or neurologic findings.

The authors' case was a male, 21 years of age, with gradually increasing symptoms during the last 2 years. He had intermittent paresthesias, pain and weakness in the right arm caused by flexion or abduction of the right shoulder to more than 90 degrees. Lowering of the arm relieved all symptoms.

There was a hard mass below the right clavicle measuring 7×4 cm. due to an anomalous first rib and a pseudoarthrosis between it and the second rib. Both ribs showed fusiform enlargement at this level and a cartilaginous plate connected them.

Blood pressure was equal in the two arms and pulses were good but disappeared with the costoclavicular maneuver (shoulder girdle thrown posteriorly and inferiorly) and pectoralis venous distention then occurred.

Vascular studies showed complete occlusion of the subclavian vein and moderate compression of the artery at the level of the bony mass when there was hyperabduction and in the anatomic position they were normal.

Surgery confirmed the roentgen changes and resection of the mass relieved all symptoms.—*Martha E. Mottram, M.D.*

Booth, J. B., and Berry, C. L. Unilateral pulmonary agenesis. *Arch. Dis. Childhood*, Aug., 1967, *42*, 361–374. (From: The Hospital for Sick Children and the Institute of Child Health, Great Ormond Street, London W. C. 1., England.)

The authors report 17 cases of unilateral pulmonary agenesis. Of their cases, 8 are still living and have been followed from infancy. They describe in detail the associated abnormalities and they compare their cases with those recorded in the literature. In particular, an increased percentage of ipsilateral abnormality was noted.

Using chest roentgenography, it was found that in left-sided agenesis the heart and mediastinum are shifted markedly to that side and there may or may not be aeration of the apical and paravertebral areas on the affected side, depending on the degree of hypertrophy of the opposite lung. In right-sided agenesis there is apparent dextrocardia and often herniation of the left lung across the anterior or posterior mediastinum.

On the side of the agenesis it is usual to observe the ribs placed closer together and having imbricated appearance.

Bronchography confirms the type and degree of the malformation.

On angiocardiography, no pulmonary artery is

demonstrated on the affected side in true agenesis. However, when a pulmonary blood flow is shown some lung tissue must be present and the condition should be regarded as one of pulmonary hypoplasia.

The authors give a detailed report of associated abnormalities.—*Lionel W. Young, M.D.*

PEARSON, J. B., and GRAY, J. G. Oesophageal hiatus hernia: long-term results of the conventional thoracic operation. *Brit. J. Surg.*, June, 1967, *54*, 530–533. (From: Department of Surgery, Queen Elizabeth Hospital, Birmingham, England.)

The authors have collected a number of cases reported in the past, and have tabulated the results as to recurrences, length of follow-up, and the comments of the various investigators. They have accumulated quite an imposing series.

In an analysis of their own cases the authors have reviewed an average period of 6½ years following surgical repair, comprizing 64 patients. Eighty-three per cent are symptomatically improved, while only 40 per cent are radiologic successes.

A summary of the surgical technique is presented. —*David C. Alftine, M.D.*

LOWE, WILLIAM C., and PALMER, EDDY D. Esophageal stricture as a complication of gastric surgery. *Am. J. M. Sc.*, Sept., 1967, *254*, 342–346. (From: The Division of Gastroenterology, Department of Medicine, New Jersey College of Medicine and the Veterans Administration Hospital, East Orange, N. J.)

The authors report 6 patients who developed benign cicatricial esophageal stenosis as a complication of gastric surgery. Four patients had partial gastrectomy and 2 had vagotomy.

Dysphagia developed 1 to 7 weeks after operation. The diagnosis of stricture was confirmed by barium swallow, esophagoscopy and repeated biopsies which showed acute and chronic inflammation.

The duration of the indwelling nasogastric tube following surgery varied from 2 to 21 days, suggesting that the mucosal trauma by the intubation and persistent regurgitation might be the chief cause of the stricture.

Treatment with Hurst bougienage was successful in all patients and surgical treatment was never considered.—*C. Peter Truog, M.D.*

ABDOMEN

MEYERS, MORTON A. Gastroduodenal intussusception. *Am. J. M. Sc.*, Sept., 1967, *254*, 347–356. (From: Department of Radiology, The Bronx-Lebanon Hospital Center, Fulton Avenue at 169th Street, Bronx, N. Y. 10456.)

The author reviewed the world literature and found 55 instances of reported gastroduodenal intussusception; he adds 2 cases of his own to bring the total to 57.

The apex of the invagination is almost invariably formed by a gastric tumor which carries with it a portion or entire circumference of the full thickness of the stomach wall into the duodenum, occasionally as far as the ligament of Treitz or distally into the jejunum. The most common gastric tumors include adenomatous polyps arising from the antral region and leiomyomas arising in the upper half of the stomach.

Of the gastric tumors forming the apex of the intussusception, there were 21 adenomas or fibroadenomas, 8 cases of multiple adenomas or frank polyposis, 2 papillomas, 13 leiomyomas or fibromyomas, 2 neurogenic tumors, 1 lipoma, 1 fibroma, 1 possible argentaffinoma and only 4 infiltrative malignancies.

The criteria for the specific roentgenologic diagnosis of gastroduodenal intussusception depend upon recognition of both the tumor mass and the alterations produced by the invagination of the stomach wall into the duodenum. The characteristic findings include foreshortening of the distal portion of the stomach, marked widening of the duodenum with an intraluminal filling defect, converging axial mucosal folds of the gastric intussusceptum and parallel "coil-spring" folds within the duodenal intussuscipiens, a pre-pyloric collar-shaped pouch and widening of the pyloric canal. Delayed gastric emptying and changes in position of the intraduodenal filling defect during the upper gastrointestinal series may be present.—*C. Peter Truog, M.D.*

LEWIS, G. J. T. Unusual features of primary duodenal cancer. *Brit. J. Surg.*, July, 1967, *54*, 633–636. (Address: McIntyre Research Fellow, Peripheral Vascular Unit, Glasgow Royal Infirmary, Glasgow, Scotland.)

Primary duodenal cancer is rare. Its incidence in a series of general autopsies has been reported as 0.03 per cent and 0.047 per cent. It comprizes 0.3 per cent or 1 per cent of all gastrointestinal cancers and approximately 45 per cent of all small intestinal cancers.

The British literature contains reports of 16 cases of primary duodenal cancer. The disparity between these 16 cases and the large numbers reported in the American literature suggests that many so-called ampullary cancers have not been reported here, and that duodenal cancer is not necessarily rare. Suprapapillary and infrapapillary cancers are uncommon. The author reports 3 cases of primary duodenal cancer which were found in one general surgical unit during 1963–1965.

No apparent relationship to duodenal ulceration is evident.

Macroscopically the duodenal cancer may take the form of a papilliferous mass or a flat, ulcerating, infiltrating lesion. Histologic examination usually shows a columnar cell carcinoma but squamous cell metaplasia may occur.

The clinical features vary according to the type and site of the cancer. No pathognomonic symptoms can be noted. The tumor is often large before symptoms occur.

Intestinal obstruction may be intermittent due to edema, intussusception or bolus obstruction.

In the normal subject some protein loss occurs from the stomach and the jejunum. Excessive protein loss is observed in a variety of conditions. Those of surgical interest are ulcerative colitis and Crohn's disease, portal hypertension, constrictive pericarditis and atrial septal defects, intestinal lymphangiectasis, and primary carcinoma of the esophagus, stomach, and colon. A protein-losing state is not a feature of primary or secondary celiac syndrome; where malabsorption and protein-losing enteropathy coexist a gluten-free diet may restore protein metabolism to normal. Following surgical correction of the underlying lesion, protein metabolism usually returns to normal.

The results of surgical treatment for duodenal cancer were disappointing.—*Stephen N. Tager, M.D.*

WATT, J. KENNEDY, WATSON, W. C., and HAASE, S. Chronic intestinal ischaemia. (Glasgow, Scotland.) *Brit. M. J.*, July 22, 1967, *3*, 199–202.

Thrombosis of the superior mesenteric artery produces a mortality rate of about 100 per cent in untreated cases and over 90 per cent in most surgically treated cases.

The time to save these patients is before the acute episode. Chronic intestinal ischemia should be strongly suspected in middle-aged patients with atypical abdominal pain and loss of weight, especially when alimentary carcinoma is suspected and barium studies are negative.

The authors report 5 cases of their own, with successful operative intervention. The laboratory and the clinical findings are well documented.—*David C. Alftine, M.D.*

ANDERSON, RAYMOND E., WOODWARD, NEIL., DIFFENBAUGH, WILLIS G., and STROHL, E. LEE. Gallstone obstruction of the intestine. *Surg., Gynec. & Obst.*, Sept., 1967, *125*, 540–548. (From: Department of Surgery, Cook County General Hospital, Chicago, Ill.)

From 1934 through 1964, 28 patients with gallstone obstruction of the intestine were operated upon at Cook County Hospital.

The incidence, pathology, symptoms, diagnosis and treatment are discussed.

The authors present the criteria for roentgenographic diagnosis. These are: (1) presence of air in the biliary tree; (2) visualization of a gallstone in the intestine; (3) distention of the small bowel; and (4) change in the position of a stone which had already been demonstrated roentgenographically.—*Richard P. Taylor, M.D.*

KRAFT, ERNEST, and FINBY, NATHANIEL. Megasigmoid and the megasigmoid syndrome. *G. P.*, Oct., 1967, *36*, 104–114. (Address: Dr. Ernest Kraft, Veterans Administration Hospital, Northport, N. Y.)

The authors state that megasigmoid denotes a localized form of megacolon, congenital or acquired, while the megasigmoid syndrome is always acquired and consists of a triad of a large sigmoid, loss of anal sphincter tone and coexisting neuropathy involving the autonomic nervous system. The syndrome should be differentiated from the so-called "psychogenic megacolon" of elderly patients. Although predominantly observed in neuropsychiatric patients, it may also occur without a preceding psychosis. Serious complications are impaction with fecalomas, secondary toxemia, perforation of ulcers and sigmoid volvulus.

The authors believe that the megasigmoid of this syndrome is roentgenologically indistinguishable from the other types of megasigmoid. However, the megasigmoid syndrome is permanent and irreversible, whereas megasigmoid may either progress to involve the entire colon or return to normal size after successful therapeutic measures.—*C. Peter Truog, M.D.*

GLOTZER, DONALD J., STONE, PHILLIP A., and PATTERSON, JAMES F. Prognosis after surgical treatment of granulomatous colitis. *New England J. Med.*, Aug. 10, 1967, *277*, 273–279. (From: Departments of Surgery and Medicine, Tufts University School of Medicine and the New England Medical Center Hospitals, Boston, Mass. 02115.)

A distinction is made between the condition known as ulcerative colitis and the disease entity sometimes known as granulomatous colitis (Crohn's disease of the colon). For purposes of analysis the patients were placed in 3 groups: Proved granulomatous colitis, clinical granulomatous colitis and ulcerative colitis. Of the series, 48 cases were considered to be ulcerative colitis, 15 proved granulomatous colitis, and 9 clinical granulomatous colitis.

The prognoses of ulcerative colitis and regional enteritis or ileocolitis after surgical treatment are quite different. In ulcerative colitis the patient is probably cured of his intestinal disease by operation; however, in regional enteritis recurrence is to be expected in at least 50 per cent of the cases. For this reason the avoidance of operation at all costs is

justified in granulomatous colitis. If surgery is undertaken, total colectomy should be the treatment of choice.

Very few recurrences were found in the current study where the ultimate results for both ulcerative and granulomatous colitis treated by ileostomy and colectomy were studied.—*David C. Alftine, M.D.*

SEAMAN, WILLIAM B., and BRAGG, DAVID G. Colonic intramural barium: a complication of the barium-enema examination. *Radiology*, Aug., 1967, *89*, 250–255. (Address: 622 W. 168th Street, New York, N. Y. 10032.)

An unusual complication of the roentgenographic examination of the colon results from mucosal rupture and dissection by the barium solution into the wall. Usually, no symptoms are associated with the initial tear, but pain and tenderness occur minutes to hours later. The roentgenographic appearance of intramural barium is characteristic and easily recognized—a transverse striated pattern. This is probably produced by the inner circular layer of muscle fibers which are outlined by the barium solution.

Three cases of this condition are reported.

The roentgenographic procedures in the above cases were completed without noticing anything unusual, and symptoms occurred later. Two cases showed rupture in the rectosigmoid area, the other occurred in the cecum.

It is explained that the rupture of the colonic mucosa is not due to an abnormal elevation of intraluminal pressure alone, but must be related to the presence of a mucosal defect.

Spontaneous perforations have been reported in patients with normal colons. These ruptures usually occur in the rectosigmoid area. A most probable pathogenesis for this type of perforation is impaction of a hard fecal mass which produces ischemic necrosis in the wall and eventual tearing. This would explain their prevalence in the distal colon.

It is stressed that colonic intramural barium is a relatively benign complication and treatment may be conservative.—*P. M. Kroening, M.D.*

SHAW, ANTHONY, COOPERMAN, AVRAM, and FUSCO, JULIA. Gas embolism produced by hydrogen peroxide. *New England J. Med.*, Aug. 3, 1967, *277*, 238–241. (From: The Pediatric Service of the Department of Surgery and the Department of Pathology, St. Vincent's Hospital and Medical Center of New York, New York, N. Y. 10011.)

The authors report a case in a newborn infant of intestinal gangrene following colonic lavage with hydrogen peroxide. This occurred during surgical treatment of meconium ileus. They observed gas embolism of the mesenteric vessels during lavage. In experimental studies on puppies and dogs they show that hydrogen peroxide lavage of the bowel in concentrations greater than 0.75 per cent is regularly associated with gas embolism.

The authors review the literature on this subject and specifically mention the case reported by Brodeur, wherein, after transverse colostomy of a 5 month old infant, colonic lavage was carried out with dilute hydrogen peroxide. A roentgenogram of the abdomen revealed lucent streaks in the liver shadow caused by gas in the portal vein.

In the experimental studies carried out they noted that dogs having bowel lavage with solutions of 0.75 per cent or greater concentrations of hydrogen peroxide developed bubbles of air in the mesenteric lymphatics, mesenteric veins, mesenteric arteries and lymph nodes, and in many in the portal veins. Roentgenographic examinations of some of the bowel segments dramatically demonstrated gas in the mesenteric and bowel wall vessels, and in the excised liver total replacement of portal blood by gas was found.

The mechanism of the development of gas embolism is discussed. On the basis of the clinical and experimental data, the authors urge that the potentially dangerous practice of colonic lavage with hydrogen peroxide be abandoned.—*Lionel S. Young, M.D.*

WEBB, A. JOHN, and DAWSON-EDWARDS, P. Malignant retroperitoneal fibrosis. *Brit. J. Surg.*, June, 1967, *54*, 505–508. (From: Queen Elizabeth Hospital, Birmingham, England.)

Several reports indicate that idiopathic retroperitoneal fibrosis has been mistaken at operation for a malignant process.

Conversely the major differential diagnosis in a patient with possible idiopathic fibrosis is disseminated malignancy. The resemblance extends to clinical, radiologic, and operative findings. Where a desmoplastic reaction develops, the ureters frequently become involved in a diffuse retroperitoneal plaque.

From this series of 16 examples of retroperitoneal fibrosis, 3 were of malignant origin, demonstrating diagnostic difficulties identical with the non-malignant group.

Two patients are reported in detail to illustrate the problems encountered.

In a male, aged 51 years, an intravenous pyelogram by infusion demonstrated bilateral hydronephrosis and hydroureter. Barium meal examination indicated an extensive mass impinging on the greater gastric curvature, with widening of the duodenal loop. Translumbar aortography did not show an aortic aneurysm. A lymphangiogram revealed gross lymphatic obstruction with filling defects in the paraaortic and mesenteric lymph nodes. Retroperitoneal fibrosis secondary to malignancy was diagnosed and operation on January 8, 1965, confirmed

a vast fibrotic retroperitoneal plaque extending from above the diaphragm to the pelvis. Multiple biopsies were taken and immediate cytologic examination performed. He died soon afterwards and at autopsy the primary source was elusive. The liver and lumbar vertebrae were involved by malignancy. The pancreas, kidneys, ureters, great vessels, etc., were enveloped by fibrotic malignant tissue—an appearance very similar to idiopathic retroperitoneal fibrosis. Invasion and disruption of the ureteric wall was found. A small area of superficial malignant ulceration of the cardia was finally implicated. Histology showed an anaplastic linitis plastica with some mucin production.

A second similar case is also reported in detail.

The ureterogram in both patients differed little from that seen in benign fibrosis; extrinsic obstruction, medial deviation, and tapering were all present. Widening of the duodenal loop was a feature in favor of malignancy.

The lymphangiographic findings were valuable and the flow of lymph above the level of L 4, the gross lymphatic obstruction, and the filling defects in the mesenteric and paraaortic lymph nodes were against a diagnosis of benign fibrosis.

As a means of rapid diagnostic confirmation, tissue cytology, using an imprint and smear technique, was performed in both patients.

Aortic and iliac aneurysms may initiate a local fibrotic reaction and must be considered in the differential diagnosis of idiopathic retroperitoneal fibrosis.

The similarity both in presentation and operative findings between the malignant and non-malignant type is emphasized.—*Stephen N. Tager, M.D.*

Webb, A. John, and Dawson-Edwards, P. Non-malignant retroperitoneal fibrosis. *Brit. J. Surg.*, June, 1967, *54*, 508–518. (From: Queen Elizabeth Hospital, Birmingham, England.)

Although a well established clinical entity, retroperitoneal fibrosis is still overlooked and remains somewhat of a mystery. There is no generally accepted view as to what constitutes this fibrotic condition.

Terminology. This is extensive and the following is a selection of terms: (1) Inflammatory retroperitoneal process; (2) idiopathic retroperitoneal fibrosis; (3) retroperitoneal sclerosing lipogranuloma; (4) retroperitoneal granulomatous fibrosis; (5) retroperitoneal vasculitis; (6) periureteritis plastica; (7) perinephritis plastica; (8) periureteritis obliterans; (9) periureteric fibrosis; (10) perirenal (Gerota's) fascitis; and (11) pericystitis plastica.

Some descriptions, *e.g.*, pericystitis plastica, emphasize a particular location, whereas others express the authors' view as to etiology.

Clinical Features. Involvement of the urinary tract with or without anuria is the mode of presentation in most cases.

The present series, collected from Birmingham over the past 16 years totals 14 patients, of whom 10 have been seen since 1963. All are examples of non-malignant retroperitoneal fibrosis, a term preferred to 'idiopathic.' In at least 3 patients, the factor initiating the fibrosis is probably known.

All but 2 were subjected to surgical exploration to confirm and treat the condition. Full biopsy examinations are available. Two cases were discovered at postmortem examination. The details of each case in the series are presented.

The study confirms the significance of the symptom complex: persistent backache, lower abdominal and groin pain, raised erythrocyte sedimentation rate, and hypertension.

From the clinical point of view the series demonstrates that retroperitoneal fibrosis can present in many guises and that mistakes are made both in diagnosis and management. In essence, with any vague illness of gastrointestinal upset with backache extending into the lower abdomen and groins, accompanied by changes in the erythrocyte sedimentation rate and serum proteins, the diagnosis should be seriously considered.

Roentgen Findings. Intravenous pyelography and in particular the ureterogram may present an appearance almost pathognomonic. The findings may be briefly summarized as follows: 1. Delayed excretion with hydronephrosis and hydroureter above an obstruction. 2. Medial deviation and irregularity of the ureter at the level of obstruction, and often a genu, with narrowing and cone-like tapering.

Lymphangiography appears to have a definite place in the diagnosis of retroperitoneal fibrosis. The important features are: 1. Delay in passage of dye through the paraaortic lymph nodes and vessels. 2. Dilatation of lymphatics beyond the normal maximum of 2 mm. diameter. 3. Block to lymphatic flow at the L 3 level. 4. Small filling defects may be seen in the mesenteric and paraaortic lymph nodes.

Surgical Considerations. The authors recommend a transperitoneal operation, inspecting and freeing both ureters if necessary. This has been adopted in the last 6 patients of this series and found to be eminently satisfactory.

Ureteric Invasion and Reinvasion following Ureterolysis. This was found in practically all the cases. The distribution may be diffuse or nodular in form.

Cytologic Assessment. The histology of retroperitoneal fibrosis is not fully understood. Cells described as reticulum cells and bizarre invasive fibroblasts are mentioned. Peri- and para-arterial inflammatory cells have been observed in many biopsy specimen sections.

Etiology. An immunologic sensitivity response is considered to be the basis of most idiopathic cases. The sensitizing agent is probably a drug acting as a chemical hapten. A number of etiologic factors are

at work ranging from prostatovesiculitis and progressive fibrosis from traumatic pancreatitis to a hemorrhagic state.

Case Reports. The 14 cases are reported in detail. The condition remains a diagnostic problem even though the pyelographic appearances are clear cut.

Conclusion. The danger of permanent renal damage is considerable. Surgical intervention involving ureterolysis and peritoneal transposition of the ureters is the treatment of choice.—*Stephen N. Trager, M.D.*

Jose, John S. Idiopathic retroperitoneal fibrosis: notes on its diagnosis, management and pathogenesis. *Brit. J. Urol.*, Aug., 1967, *39*, 431–443. (From: Department of Urology, St. Thomas' Hospital, London, England.)

Since the initial description, over 140 cases of idiopathic retroperitoneal fibrosis have been reported in the literature.

The following report discusses some insights into the diagnosis, management, and pathogenesis of this entity obtained during the management of 5 cases at St. Thomas's Hospital, London, in the past 5 years.

Diagnosis. The diagnosis of this condition depends on the clinical awareness of the examiner. The initial presentation may be nonspecific with symptoms such as backache, low grade fever, anemia, nausea, malaise or weight loss and may not relate directly to the urinary tract. On the other hand, it may present with alteration of urine output such as oliguria or anuria and may be accompanied by azotemia. Even though the fibrotic lesion is slowly progressive, the onset of anuria may be quite rapid.

The only consistent abnormal laboratory value has been the elevated erythrocyte sedimentation rate which also has been observed to parallel the fluctuations in the patient's clinical condition. The urinalysis is usually negative initially, although transient proteinuria or pyuria has been observed.

Intravenous pyelography reveals nonfunction or hydronephrosis. Retrograde pyelography demonstrates the characteristic dilated proximal ureters tapering to a narrowed segment in the mid ureter and medial deviation at this level. The ability of the catheter to pass beyond the point of apparent obstruction with relative ease is in itself suggestive of the diagnosis. Ureteral catheter may also be used to re-establish urinary drainage and correct azotemia prior to a definitive procedure.

Management. Although nonoperative measures such as radiotherapy, steroids, and phenylbutazone have been utilized, the method of choice at this institution is ureterolysis by a retroperitoneal approach with wide lateral displacement of the ureters. This approach offers a long segment of ureteral mobilization and presumably less chance for recurrence. Intraperitoneal transposition of the ureters is used when it is felt desirable to know the total extent of the fibrosing process.

Pathogenesis. In idiopathic retroperitoneal fibrosis the chronic inflammatory fibrous tissue totally encases the involved segment but does not invade the ureteral wall; thus a true mechanical obstruction, such as seen in carcinoma, is not present. Rather, the fibrous tissue inhibits peristalsis leading to inadequate drainage of the renal pelvis and elevation of the intrapelvic pressure. This functional obstruction produces the hydronephrosis seen. Corroborating evidence is provided by experimental studies in which only peristalsis is inhibited. Peristalsis may resume after treatment however, as was seen in a 6 month follow-up in one of the cases presented.—*Major Edward Savolaine, MC, USA*

Webb, John, and Dawson-Edwards, P. Fulminating retroperitoneal fibrosis with pericystitis plastica. *Brit. J. Urol.*, Aug., 1967, *39*, 444–449. (Address: Dr. John Webb, Consultant Surgeon, Bristol Royal Infirmary, Bristol 2, England.)

In the usual course of events idiopathic retroperitoneal fibrosis presents with bilateral ureteric obstruction from a relatively localized area of retroperitoneal fibrotic plaque. The onset of the disease may be gradual or acute obstruction may develop over a period of a few weeks. The authors report a case showing unilateral disease, with abrupt onset, fulminating course, and systemic manifestations.

The patient, a 36 year old diabetic male, developed a bizarre acute illness which resembled infectious mononucleosis. Symptomatology included generalized lymphadenopathy, low grade fever, and hepato-splenomegaly. Following these symptoms prostato-vesiculitis developed together with intermittent priapism. Laboratory studies revealed *E. coli* in the urine and adeno virus in stool culture and blood titer. Intravenous pyelography demonstrated right hydronephrosis and obstruction in the mid-ureter with medial angulation at the level of obstruction. Cystoscopy showed mucosal ulceration and a mass invading the bladder wall. Lymphangiography revealed large iliac and inguinal lymph nodes with a block of the lymphatics at the level of the ureteral obstruction.

Surgery was performed and retroperitoneal fibrosis was found extending from above the renal vessels into the pelvis and involving the perivesicular tissues. An additional diagnosis of pericystitis plastica secondary to the retroperitoneal fibrosis was made.

Only 12 cases of similar bladder involvement are recorded in the literature and only 1 other case with as florid a symptomatology.

A discussion of the histologic and cytologic findings is presented and attention is called to rather active histiocytic proliferation and invasive fibro-

blastic metaplasia seen in some cases. The reactive hyperplasia of the lymph nodes in this case histologically resembled early Hodgkin's disease in some respects. The resemblance between the above findings and those of a hypersensitivity reaction is pointed out as in accord with the observations of some other authors.

The role of infection as a possible etiologic factor rather than a consequence of ureteric obstruction is discussed in the light of the sequence of events in this case and the fact that sever diabetics are prone to genital infections.—*Major Edward Savolaine, MC, USA*

HADDOW, R. A., and KEMP-HARPER, R. A. Calcification in the liver portal system. *Clin. Radiol.*, July, 1967, *18*, 225–236. (From: St. Bartholomew's Hospital, London, England.)

Calcification in the portal system and liver is uncommon. Three patients in whom portal calcification was found are described by the authors. In cases in which the calcification is rather nonspecific in type diagnosis can be made only by splenoportography. If the calcification is extensive it should be recognizable on a flat roentgenogram of the abdomen because of the position and extent of the linear shadows crossing the vertebral column.

Calcification in liver tumors is relatively uncommon. The calcification is usually of a mottled and nonspecific type. Since about 80 per cent of hepatomas and about 50 per cent of cholangiomas are associated with cirrhosis, the finding of calcification in the liver of a known cirrhotic patient is apt to be of serious prognostic significance. Calcification in a gumma of the liver is extremely rare.

The causes of hepatic calcification listed by the authors are: (1) Calcification in a hydatid cyst; (2) calcification in liver metastases; (3) calcification in primary liver tumors; (4) calcified aneurysm of the hepatic artery; (5) calcified liver abscess; (6) calcified tuberculous or histoplasmosis nodules; (7) calcified brucellosis granulomata; (8) calcified gumma: and (9) hepatic stones.

The authors report 3 patients in whom portal calcification was found, in 1 with associated portal cirrhosis, and in 2 with portal hypertension due to thrombosis of the portal vein. Three patients with calcification in the liver were also seen: 1 with primary carcinoma of the liver, 1 with a bile duct carcinoma and the third with a gumma of the liver.—*Samuel G. Henderson, M.D.*

GYNECOLOGY AND OBSTETRICS

ADLER, JOEL B. and PATTERSON, ROBERT L., JR. Erb's palsy: long-term results of treatment of eighty-eight cases. *J. Bone & Joint Surg.*, Sept., 1967, *49A*, 1052–1064. (Address: Dr. Joel B. Adler, Kohl Building, Route 59, Suffern, N. Y.)

The incidence of Erb's palsy has decreased steadily from 1938 to the present. Eighty-eight of 123 patients seen at the Hospital for Special Surgery from 1939 to 1962 were available for follow-up with an average interval of 18 years and a range of 1 to 35 years.

The incidence of Erb's palsy is related to the degree of difficulty of delivery and the birthweight. Only 13 of 123 patients were said to have had normal deliveries and 56 were reported as difficult; breech delivery occurred in 9 per cent. The 4 patients with bilateral Erb's palsy were all breech deliveries. The birthweight averaged 9 lb. 8 oz., with a 5–16 lb. range.

The diagnosis is made clinically when there is no active motion of the shoulder but equal passive motion of both shoulders. Roentgenograms should always be obtained to exclude skeletal injury.

The authors discuss the necessity of early diagnosis, various treatment methods and their late results. The most important early treatment is prevention of contractures.

The roentgen findings include molding of the humeral head and glenoid in patients with a fixed internal rotation and adduction contracture. Three problems involve the elbow: (1) flexion contracture which may be related to original trauma or the effects of early bracing; (2) posterior dislocation of the radial head; and (3) a progressive disruption of the entire elbow joint with medial and posterior dislocation of the ulna, flattening of the trochlea, angulation of the proximal radial metaphysis, dislocation of the radial head and increased curvature of the ulna. Treatment in this latter condition has been entirely unsuccessful. Thirty-eight of the 88 patients had some elbow deformity.—*Martha E. Mottram, M.D.*

JOHNSON, PHILIP M., SCIARRA, JOHN J., and O'LEARY, JAMES A. Placental scanning with sodium pertechnetate Tc^{99m} serum albumin. *Radiology*, August, 1967, *89*, 321–323. (Address: 622 W. 168th Street, New York, N. Y. 10032.)

Since the site of the placenta, especially in relation to the lower uterine segment, is a major consideration in the management of vaginal bleeding during the third trimester of pregnancy, the obstetrician must determine its location if he is to decide if placenta previa is present. Placental localization using radioisotopes is now considered the method of choice in many centers because it is accurate, simple and safe. The amount of radiation delivered to the fetus and maternal gonads is far below that from roentgenographic methods. The established isotopic method depends on detection of a radioactive tracer in the placental blood pool by multiple point counts taken over the abdomen with a scintillation probe. The isotopes of iodine and

chromium which are commonly used are sufficient for the above method, but in order that radiation doses be held to the minimum, they are unsatisfactory for high resolution scanning.

Sodium pertechnetate Tc^{99m} bound to serum albumin has the favorable physical characteristics—6 hour half life and absence of significant beta radiation—which result in a very low absorbed radiation dose. Thus, it can be given in doses sufficient to perform scintillation scanning, a method which is potentially better than multiple point counting.

This report describes the results of placental localization by using sodium pertechnetate Tc^{99m} serum albumin and scintillation scanning in 36 gravid patients. The procedure is presented in detail. The anatomic site of the placenta was correctly predicted in 34 patients. In the 2 patients who were incorrectly diagnosed, one was a posterior partial placenta previa thought to be a low fundal implantation, while the other was a low fundal implantation erroneously diagnosed to be a placenta previa. All 36 pregnancies resulted in delivery of viable fetuses. There were no untoward reactions observed.

Two illustrative cases are reported. It is stressed that trapping of free radioactive pertechnetate Tc^{99m} by maternal and fetal thyroid tissue be minimized by expanding their iodide pools (iodide ions compete with pertechnetate ions) or blocking their uptakes with potassium perchlorate. Also, the isotope generator must be pyrogen-free.

It is calculated that the radiation dose from a 1,000 μc injection of this isotope is 5 millirads to the maternal whole body and 14 millirads to the fetal whole body, and that 3 per cent of the radioactivity crosses the placental barrier into the fetal circulation. —*P. M. Kroening, M.D.*

RAITI, S., HOLZMAN, G. B., SCOTT, R. L., and BLIZZARD, R. M. Evidence for the placental transfer of tri-iodothyronine in human beings. *New England J. Med.*, Aug. 31, 1967, *277*, 456–459. (From: The Departments of Pediatrics, Obstetrics and Gynecology and Internal Medicine, Johns Hopkins Hospital and University School of Medicine, Baltimore, Md. 21205.)

The purpose of this study was to determine if tri-iodothyronine (T_3) crosses the placenta and, if so, the dosage the mother must receive if the fetal endogenous requirements are to be replaced.

Four groups of patients were studied: (1) normal pregnant women, without treatment; (2) normal pregnant women who were given either 150, 200 or 300 μg. of T_3 per day for the last 4 to 6 weeks of pregnancy; (3) athyreotic cretins who were pregnant and whose therapy was changed to T_3 for this study; and (4) normal women who were not pregnant.

Serial T_4 by column determinations on the maternal serum was used to determine the effect of T_3 on suppression of the maternal hypothalamic-pituitary-thyroid axis. With complete suppressive doses of T_3 in the normal subject, the PBI, and by assumption the T_4 by column determination, which includes the T_3 and T_4 iodine, fall into the hypothyroid range. The same determinations were done on cord serum since a fall in the cord T_4 by column would reflect the placental transfer of T_3 from mother to fetus with resulting pituitary depression.

The authors found that significant quantities of T_3 crossed the placenta in at least 50 per cent of the cases when 300 μg. of T_3 was administered to the pregnant female, and when smaller doses of T_3 were given variable and perhaps insignificant transfer of T_3 occurred. There was a marked variability of placental transfer of T_3 between maternal and fetal pairs, or alternatively, individual variation in the suppressibility of the fetal hypothalamic-pituitary-thyroid axis.—*Charles W. Cooley, M.D.*

GENITOURINARY SYSTEM

REULE, G. RONALD, and ANSELL, JULIAN S. Discordant occurrence of genitourinary defects in monozygotic twins. *J. Urol.*, June, 1967, *97*, 1078–1081. (From: Department of Urology, University of Washington Hospital, Seattle, Wash.)

The authors report 5 instances in which one of a pair of monozygotic twins demonstrated significant urologic anomalies. These anomalies consisted respectively of bilateral testicular hypoplasia, hydronephrosis with ureteral valves, bladder exstrophy, hypospadias and neurogenic bladder dysfunction. The twin of each of these individuals was normally developed.

The causes of dissimilarity between identical twins may be either genetic or environmental. One genetic mechanism may be mutation occurring late in pregnancy so as to involve only one of the two embryos. Another could be activity of cytoplasmic inheritance factors, or the absence of unknown factors which are responsible for asymmetry in an individual.

Environmental influences, such as prenatal pressure by one fetus or by the placenta or unequal placental development or blood flow during embryonic development, might account for unequal distribution of the anomalies. Toxic or infectious agents are conceivably of etiologic importance and also a combination of factors such as unfavorable environmental conditions which lower the threshold for abnormal genes.

The authors point out that instances of this type in monozygotic twins are rare, but that when they occur the normal child offers an excellent donor for organ transplantation as well as a control for the therapy delivered to the abnormal infant.

Six composite figures are used to illustrate the

defects seen in the affected children.—*George W. Chamberlin, M.D.*

RADWIN, HOWARD M., and NOVOSELSKY, SETH P. The gamma camera in pediatric urologic diagnosis. *J. Urol.*, May, 1967, *97*, 942–947. (From: Department of Surgery, Section of Urology, Tulane University School of Medicine, New Orleans, La.)

The authors discuss their experience with the Anger gamma scintillation camera in the study of pyelonephritis, renal obstruction, and renal transplantation.

The gamma camera by virtue of its ability to simultaneously scan the entire urinary tract allows the study of dynamic function rather than the morphologic appearance obtained by conventional scanners.

The authors used radiomercury 203 or 197 or radioiodinated hippuran. The latter was frequently used because of its similarity physiologically to para-aminohippurate. Exposures of predetermined length were made at specific intervals after injection of the radioisotope. In general, several 1 minute exposures were made at intervals up to 2 hours after the injection, with the majority apparently being made in the first 15 to 20 minutes. A residual scan was usually done 2 days post injection.

Obstructive disease was studied following water diuresis with hippuran being injected several minutes after ingestion of several glasses of water. It was found that the isotope rapidly cleared the normal side and was held up on the obstructed side. The area of localized obstruction was commonly identified.

Study of patients undergoing rejection crisis in transplantation showed findings similar to those seen in mild obstructive disease. Gradual accumulation of the isotope and increase rather than decline in the concentration of the material in the excretory portion of the tracing were found. This is thought to be due to accumulation of the isotope in excess of the renal capacity to evacuate it. This finding was similar to that seen in obstructive disease but is felt that sequential scans might be helpful by indicating whether the hold up was at the kidney level or at the ureterovesical junction or below.

Chronic pyelonephritis was studied under conditions of antidiuresis. There was a delay in excretion found on the involved side which was not apparent in patients studied under normal conditions or under conditons of diuresis. It is suggested that this inability of the renal collecting system to respond to low urine volume by initiating peristalsis might be an early result of chronic pyelonephritis and might precede significant clearance alterations. The technique apparently differentiates between the dilatation due to pyelonephritis and that due to obstructive disease in that in the latter delayed excretion is best seen under diuretic conditions.—*George W. Chamberlin, M.D.*

NERVOUS SYSTEM

ALKER, GEORGE J., JR., GLASAUER, FRANZ E., ZOLL, JOHN G., and SCHALGENHAUFF, REINHOLD. Myelographic demonstration of lumbosacral nerve root avulsion. *Radiology*, July, 1967, *89*, 101–104. (From: Edward J. Meyer Memorial Hospital, Buffalo, N. Y. 11215.)

The authors report 2 cases of lumbosacral nerve root avulsion secondary to traumatic separation of the sacroiliac joint. Although avulsion of the cervical roots as a result of traction injury to the shoulder girdle is well known, only 3 other myelographically proven cases of lumbosacral avulsion have been reported. The difference in incidence between nerve root avulsions at the two levels is probably related to the much greater stability of the sacroiliac joint and fixed bony pelvic mass protecting the nerve roots and preventing stretch upon them in this area as compared to the more delicate and mobile pectoral girdle.

Nerve root lacerations and contusions are more common than avulsions in fractures of the pelvis. These are often seen in sacral fractures. Sacral fractures may also result in nerve root avulsions but most lumbosacral nerve root avulsions are associated with separation of the sacroiliac joint, probably as the result of forceful shearing or peripheral nerve traction at the time of separation. Other possible mechanisms are stretching or contusion of the nerve and pressure injury to the lumbosacral nerve trunk.

The myelographic findings in these cases are the same as those seen in cervical nerve root avulsion. Pantopaque freely enters broad, often irregular, outpouchings in the subarachnoid space at the sites of the affected nerve roots. The nerve roots are not often seen. These pockets are created by tears in the arachnoid covering the nerve roots. These findings should be differentiated from the appearance of nerve root meningoceles, which are narrow-necked sacculations along the visible nerve roots. They are often bilateral, multiple and asymptomatic.

Myelography is indicated in suspected nerve root avulsions to differentiate this type of injury to the peripheral portion of the nerve, since the latter condition offers some possibility of eventual return of function following nerve repair.—*V. Brasseur, M.D.*

RADIATION THERAPY

BERGSAGEL, DANIEL E. The chronic leukemias: a review of disease manifestations and the aims of therapy. *Canad. M. A. J.*, June 24, 1967, *96*, 1615–1620. (From: The Princess Margaret Hospital, 500 Sherbourne Street, Toronto 5, Ontario, Canada.)

The author notes that therapeutic advances have improved the prognosis of patients with acute leukemias, but that the prognosis of patients with chronic lymphocytic leukemia (CLL) has not *per se* been improved. He believes that future designs for therapeutic trials should be aligned with newer pathogenic concepts of CLL.

Antimitotic agents, for instance, are poorly effective in CLL because of the indolence and longevity of the CLL lymphocyte. Investigation of CLL lymphocyte doubling time shows two distinct trends in counts monitored over many months which (despite chemotherapy) may indicate a homeostatic mechanism abnormally re-adjusted. Another characteristic property is the alteration of the patient's immune mechanism such as: (1) hypogammaglobulinemia; (2) impaired antibody formation and delayed hypersensitivity both primary and secondary, but especially the former; (3) impaired tissue culture lymphocyte transformation into "blast-like" cells after stimulation by phytohemagglutinin (PHA) and other antigens. The anemia of CLL may also be on an autoimmune basis since erythropoiesis is suppressed through interference with homeostasis rather than deficiency of erythroid precursors, and steroid therapy readily stimulates reticulocyte response.

These recent concepts would possibly indicate that the approach to therapy of CLL should not be along lines of neoplastic disease, but rather by the use of yet to be developed agents that will restore the immunologic competence of lymphocytes.

In chronic myelocytic leukemia (CML) the leukocyte doubling time decreases as the duration of the disease increases with consequent decrease in survival. Survival time is decreased in the few patients (5 per cent) with CML who demonstrate no Philadelphia chromosome. CML may arise from an abnormal hematopoietic stem cell since other somatic cells do not contain the Philadelphia chromosome. Therapy should be eventually directed at this stem cell if it can be determined that a normal stem cell coexists. At this time busulfan offers longer survival times than selective irradiation or P^{32}.—*Richard J. Torpie, M.D.*

KING, D. Radiotherapy in the management of leukemia. *Canad. M.A.J.*, June 24, 1967, *96*, 1621–1625. (From: Hamilton Clinic, The Ontario Cancer Foundation, Henderson General Hospital, Hamilton, Ontario, Canada.)

Splenic irradiation results in a rapid regression of a large, painful spleen. It has a remote effect on bone marrow by increasing the maturity of the myeloid series. It controls anemia due to hypersplenism.

Whole-body irradiation may produce remissions where splenic irradiation or chemotherapy fail. Radioactive phosphorus is an agent for administering whole-body radiation but the response to it in similar cases may vary by a factor of 10.

External radiation therapy controls localized infiltrations of leukemic cells in the central nervous system, bones, skin and other organs.

Megavoltage electron beam therapy with 4–8 mev., as a whole-body technique, controls widespread leukemic skin deposits.—*Louis H. Goldman, M.D.*

BOYD, J. T., GIBBS, D. F., LABRUM, A. H., and PHILPS, F. R. Cervical screening for carcinoma: a comparison of cytological and enzyme (6-phosphogluconate dehydrogenase) methods and clinical findings. *Brit. M. J.*, June 24, 1967, *2*, 785–792. (From: M.R.C. Statistical Research Unit, University College Hospital Medical School, London W.C. 1, England.)

Comparison of cytologic testing and 6-phosphogluconate dehydrogenase determinations of the vaginal fluid was performed on 4,385 married women attending 4 hospital and general practice clinics in order to determine the relative values of the 2 screening methods for cervical cancer.

Twenty-eight cases of carcinoma *in situ* were detected of which 67 per cent consistently showed false-negative values on enzyme determinations. Sixteen per cent of 3,439 patients without cytologic evidence of malignancy had false-positive enzyme values (100 units and above.) Enzyme values in postmenopausal women were consistently higher as were those in patients with trichomonal infection, atrophic vaginitis and other signs or symptoms of infection.

Because of the high percentage of false-negatives, the enzyme test is not considered a practical alternative to cytology for detecting preinvasive cervical cancer.—*John Thomas McMurray, M.D.*

CALAME, RICHARD J., and WALLACH, ROBERT C. An analysis of the complications of the radiologic treatment of carcinoma of the cervix. *Surg., Gynec. & Obst.*, July, 1967, *125*, 39–44. (From: The Gynecological Tumor Service, Departments of Obstetrics-Gynecology and Radiology, State University of New York Downstate Medical Center, Brooklyn, N. Y.)

Seven hundred and eighteen patients with the diagnosis of invasive carcinoma of the cervix were admitted to the Kings County Hospital between 1951 and 1964.

Eighty two per cent of the Stage I lesions were treated by radical hysterectomy and so were all patients with minimal parametrial or vaginal involvement of the ones of Stage II.

The patients treated by radiation therapy alone

had late Stage II and Stage III lesions. The radiation therapy patients are divided in 3 groups.

(1) From 1951 to 1956, 3,000 r tumor dose was delivered through 4 portals in a period of 10 to 12 weeks with a 250 kv. unit. Radium in intracavitary and contracervical doses of 6,000 to 7,000 mg.-hr. was administered before, during, or after the external therapy.

(2) From 1956 to 1962, patients with Stage I, II and IV lesions received 3,000 r and those with Stage III lesions 3,500 r to the tumor through 5 portals in a period of 4 weeks with the same apparatus. Following that, 50 mg. of radium was inserted for 100 hours; thus the whole course was accomplished in 5 weeks.

(3) From 1962 to 1964, 4,000 rads in 4 weeks were delivered by means of a cobalt 60 teletherapy unit and 6,000 mg.-hr. radium was given, fractionated in 2 applications one week apart.

(1) In the 1951–1956 group (137 patients), there were 5 rectovaginal fistulas, 5 vesicovaginal fistulas, 1 infravaginal fistula, 5 severe rectal strictures with bleeding proctitis, and 8 cases with severe bleeding cystitis—a rate of complications of 27 per cent.

(2) In the 1956–1962 group (169 patients), there were 1 vesicovaginal fistula, 4 hemorrhagic cystitis, 2 severe rectal strictures and 6 severe bleeding proctitis—a rate of complications of 10 per cent.

(3) In the 1962–1964 group (50 patients), there were 2 rectovaginal fistulas, 1 vesocovaginal fistula, and 1 severe hemorrhagic cystitis—a rate of complications of 14 per cent

The authors find a rise in serious complications following cobalt 60 therapy. Although the radium might be contributing to the complications of the midline, it is felt that cobalt 60 is the main responsible factor.—*John Antoniades, M.D.*

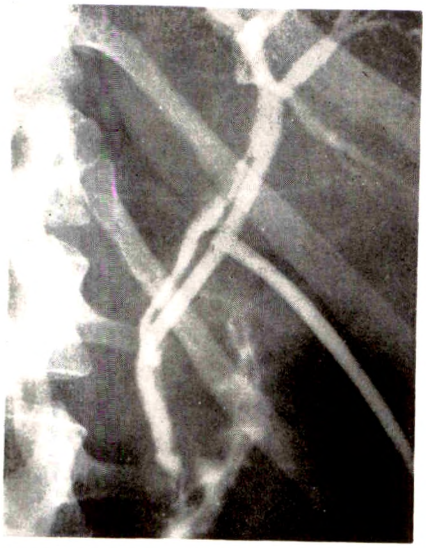
MISCELLANEOUS

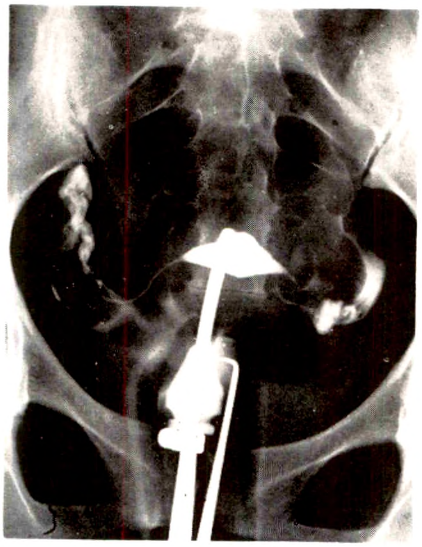
RAO, K. R. Report on Kerala (India), a region with high background radiation. *Radiol. clin. et biol.*, 1966, *35*, 373–380. (From: Strahlenbiologisches Institut der Universität, CH-8003 Zürich, Switzerland.)

This report is a review of a number of surveys conducted in South India to determine the background radiation levels and to study the effects of high natural radioactivity on inhabiting plants, animals and human population. On the South-West coast of India is a strip of monazite sand deposits which contain principally thorium. The distribution of the radioactive sand is very uneven and the most massive deposits are in two regions: one at Manavalakurchi, and the other is a stretch from Neeandakara to Kayankulum in the State of Kerala. The radiation levels range from 1.0 mr/hour to 5.0 mr/hour.

Studies on the uptake of radionuclides by plants growing in high radiation areas suggest that a significant linear relationship exists between the activity contained in plants and the radiation level. Dietary surveys were undertaken and have shown that the daily consumption of alpha activity through dietary items of plant origin ranges from 0.43 to 4.84 pc per person.

Studies of rats trapped from high radiation locations as compared with those from areas with normal background radiation failed to show any genetic abnormality. However, certain interesting chromosomal abnormalities in the blood cells of people inhabiting the high radiation area are mentioned, but the details of these are not yet published.—*Ismail Kazem, M.D.*





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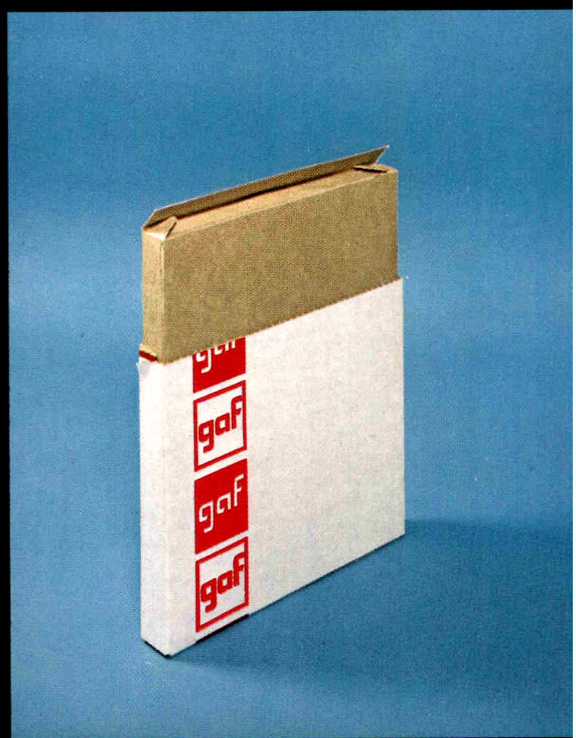
below, right The individual boxes include a full length internal sleeve that is lightproof for added safety. Reclosable top for maximum protection.



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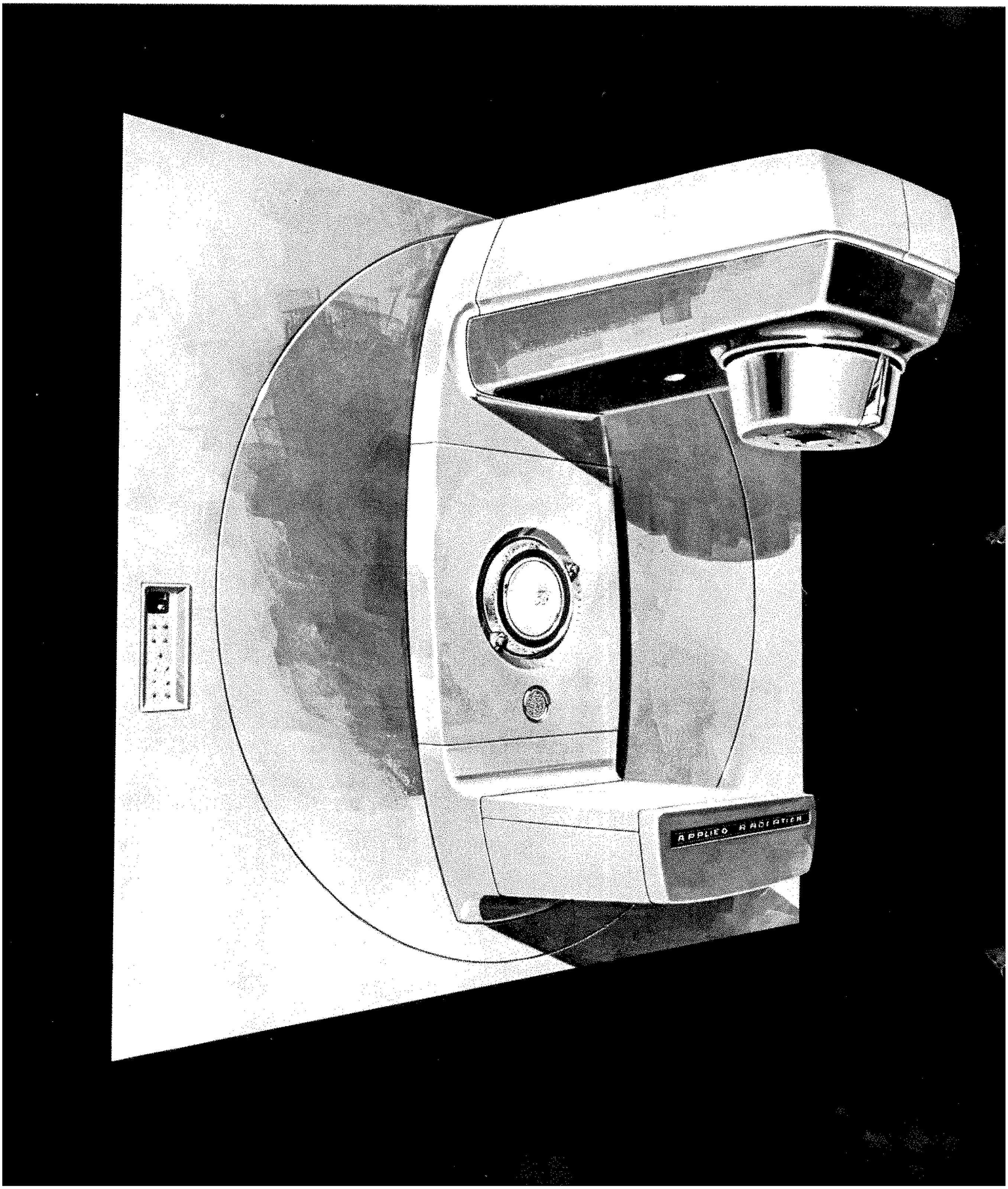

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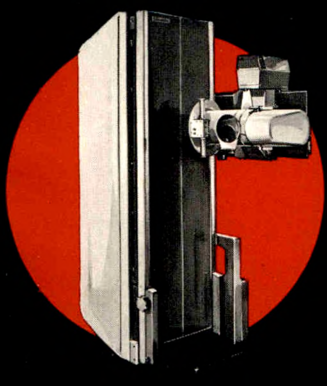

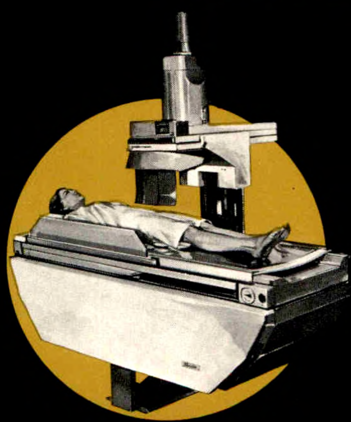

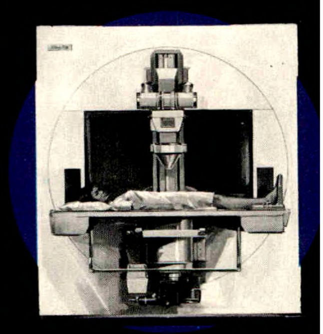

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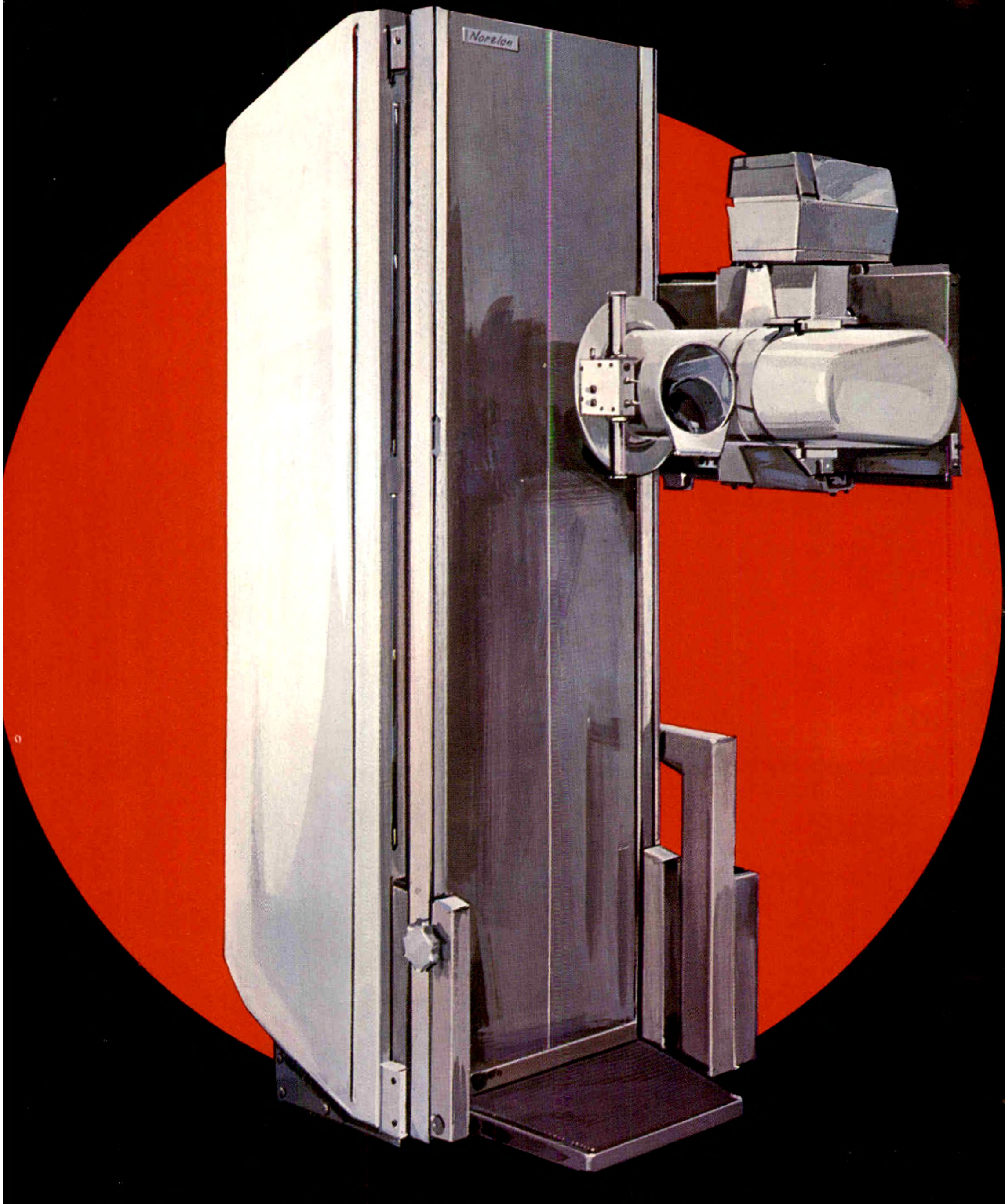

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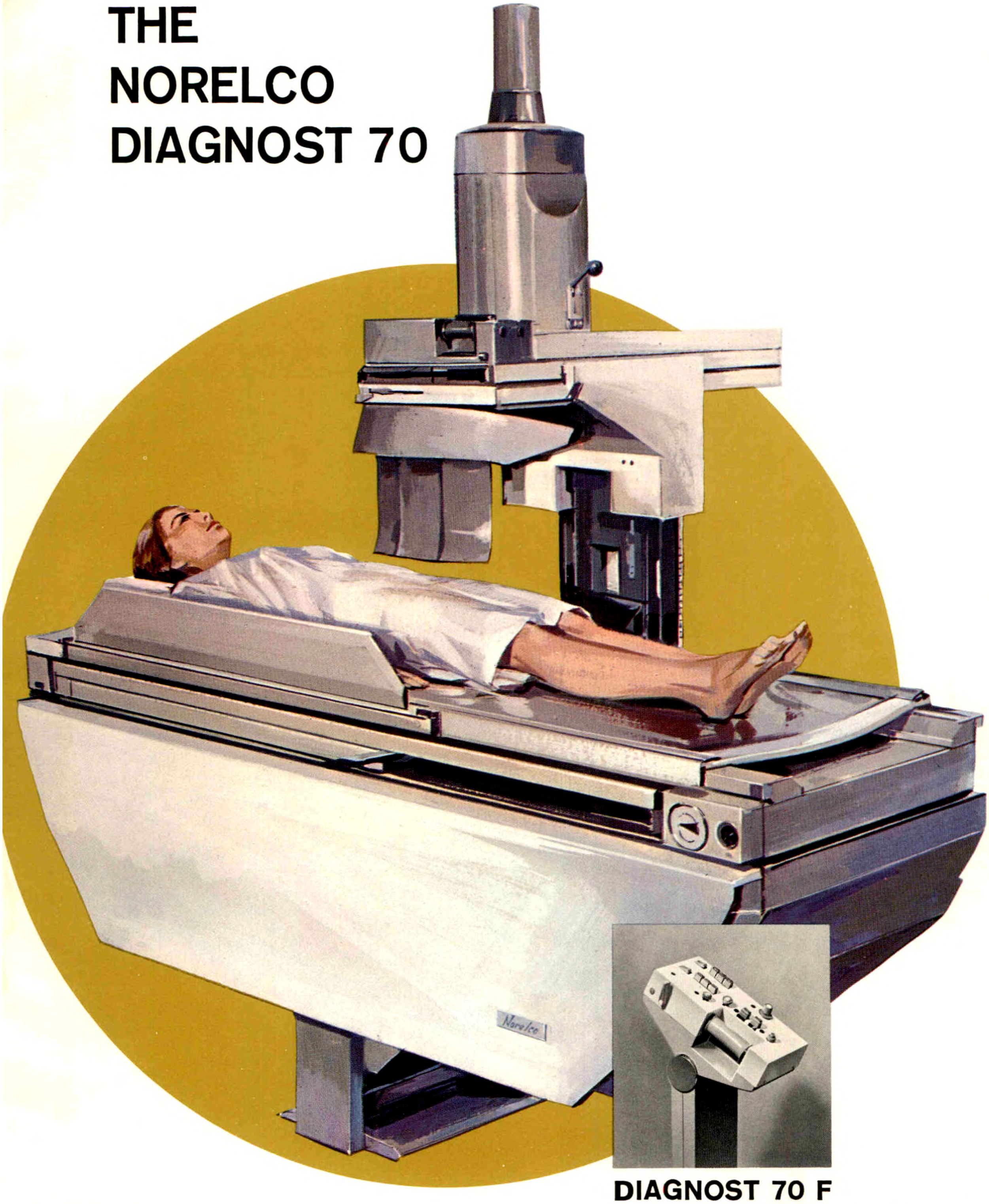

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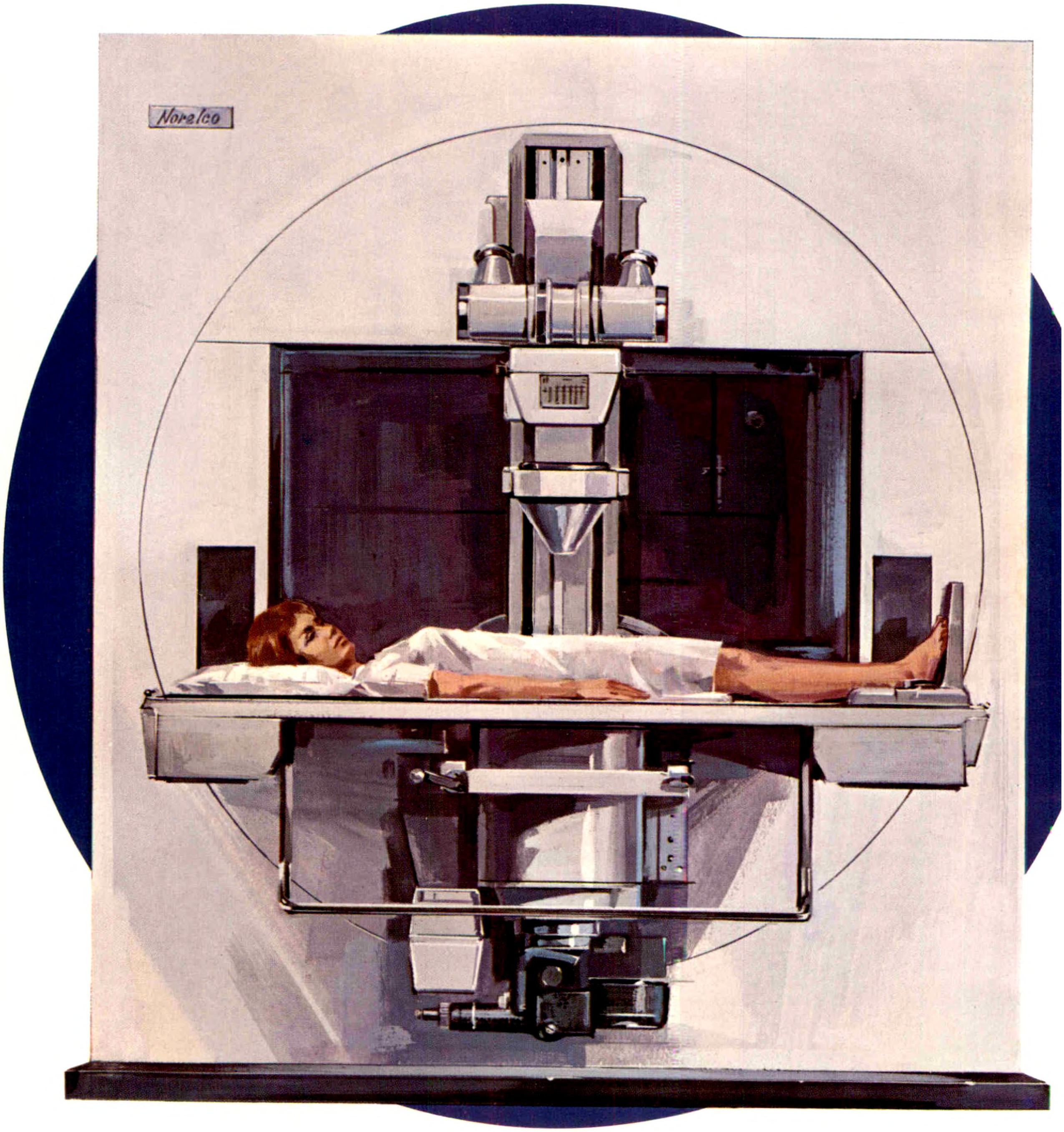

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SQUIBB

a research concept in contrast visualization

for better definition of disease: documenting differences between contrast agents

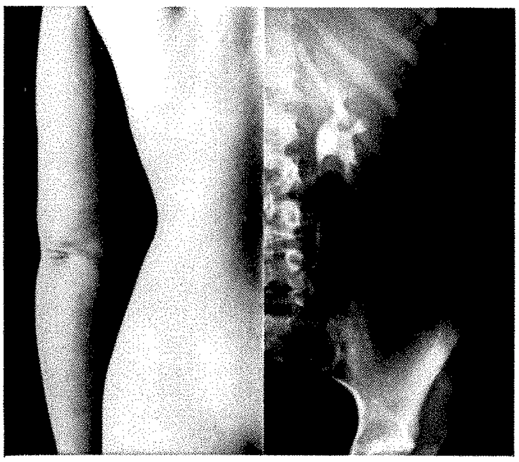
No. 1 in a series:

Renografin-60 (meglumine diatrizoate injection) preferred in a study of pyelographies of 2,234 patients.

In a new large scale study,[1] "...to determine which medium would produce adequate visualization of the urinary tract with the fewest toxic effects on the patient," Macht *et al.* have compared Renografin-60 with 2 other contrast agents.

Data were analyzed in 2,234 unselected (consecutive) patients, according to age, sex, and general disease group for the study population as a whole. The first 683 patients received 50% diatrizoate sodium solution, the next 921 patients received Renografin-60, and the final 630 patients received 66.8% sodium iothalamate solution.[1]

criteria for quality and comparative safety The contrast agents were evaluated for quality of diagnostic films as follows: films showing a dense concentration of contrast medium with filling and visualization of all major and minor calyces, infundibula, pelves and almost all of each ureter were listed as "good"; films showing less concentration with incomplete visualization of all portions of urinary tract but sufficient to produce diagnostically adequate films were listed as "fair"; films showing unsatisfactory visualization of urinary tract, or films which could not be interpreted, as "poor." The media were also evaluated as to incidence of the following side effects: nausea, vomiting, fainting, shock or severe reaction, hiccups, hives, pain in arm, sneezing, hot flushes, stuffiness of nose or ears.[1]



The following chart* shows comparative results of the 3 media according to age category:

quality of pyelograms and side effects expected in standard population of 1,000 patients by age, according to type of medium used

medium used and type of patient	standard population	quality of pyelograms good	fair	poor	with side effects
meglumine diatrizoate					
all ages,	1,000	827	123	50	41
0-19†	126	122	3	1	3
20-49	415	374	35	6	27
50-69	315	240	51	24	9
70 or older	144	91	34	19	2
diatrizoate sodium					
all ages,	1,000	782	134	84	72
0-19	126	115	6	5	7
20-49	415	378	26	11	40
50-69	315	227	64	24	19
70 or older	144	62	38	44	6
sodium iothalamate					
all ages,	1,000	883	81	36	54
0-19	126	122	4	0	7
20-49	415	393	20	2	29
50-69	315	269	32	14	13
70 or older	144	99	25	20	5

*Adapted from Macht[1] †In some patients in this age group, higher than recommended doses were used.

In theory: "The choice of contrast agent should ideally be individualized according to the age, sex, and disease group of the patient in order to obtain a high probability of complete visualization of the urinary tract with low probability of adverse side effects."[1]

In practice: "The choice is to be made...on the basis of the agent which gives the best concentration and the fewest side effects in the greatest number of patients regardless of age, sex, or disease category."[1]

In order of preference: Although Renografin-60 was not rated highest in all categories, the authors feel that their preference of the contrast media for intravenous pyelography would be: first, Renografin-60; second, sodium iothalamate; third, diatrizoate sodium.[1]

For brief summary of prescribing information, please refer to the end of this advertisement.

definition of safety...

demonstrated in animals... Since meglumine diatrizoate is also used for cerebral angiography, toxicity studies of administration via the carotid artery are therefore of interest. Fischer and Eckstein[2] designed angiographic studies in animals in which procedures were very similar to clinical angiography, and which yielded data that was quantitative, graphic and nonsubjective.[2] According to the authors: "We selected the alterations in arterial blood pressure, venous pressure, heart rate and rhythm, the electrocardiogram and end-expiratory CO_2 concentration resulting from experimental cerebral angiography as refined, sensitive indications of the toxicity of a particular contrast material."[2] Their results of measured cardiovascular functions in dogs indicated that meglumine diatrizoate was far less toxic than four other contrast media.[2] As Fischer and Cornell reported in a later study: "Despite the testing of more highly concentrated solutions and larger doses, the cardiovascular responses [in dogs] from methylglucamine [meglumine] salts were much less than from sodium salts, an observation consistent with previous experiments."[3]

Other investigators have documented the comparative safety of meglumine salts in experimental studies. In order to determine reaction and tolerance of the intestines, Cooley[4] injected meglumine diatrizoate into mesenteric arteries of dogs and found no damage. Gensini *et al.*[5] reported that cardiovascular responses with it were almost identical to blood transfusions.

theory of lower toxicity with meglumine... Gensini and DiGiorgi have offered a hypothesis to explain their findings of lesser toxicity with experimental intravascular injections of methylglucamine (meglumine) salts. "When a relatively undiluted amount of sodium salts of a contrast agent is injected in an artery and carried by the blood stream toward the capillary bed, its molecules rapidly dissociate and readily diffuse through the capillary membrane and into the tissue. There, both the toxic effect of the iodine-containing organic radical and the increased concentration of sodium will readily manifest themselves. At equal concentrations of sodium, the end results will closely reflect the intrinsic toxicity of the iodine-containing organic radical on the tissues...."[5]

"In the case of the methylglucamine compounds, the same dissociation takes place. However the larger methylglucamine molecule, rich in hydrogen bonds, apparently either limits the migration of the organic radicals outside the vessel or at least minimizes their effects on the cellular metabolism."[5]

proved in practice... Paralleling similar findings in animals, clinicians have reported a generally lower incidence of untoward reactions with Renografin-60 in urologic and cerebrovascular use. However, as with all intravascularly injected contrast agents, the possibility of severe reactions should be kept in mind (see Contraindications, Precautions and Side Effects below). In one study of over 600 urologic patients, the investigators reported that Renografin-60 produced urograms of diagnostic quality with a 6% incidence of side effects. The authors concluded: "It is hard to believe that any drug introduced intravenously could be so well borne by so many patients...."[6]

In a 74-patient study,[7] comparing Renografin-60 with diatrizoate sodium in carotid arteriography, Shealy commented: "With confused patients who are to have arteriography under local anesthesia, it is particularly desirable to have an agent that causes little pain." In this study, since "...60 per cent Renografin has resulted in considerably less pain than 50 per cent or 45 per cent [diatrizoate sodium]...we have converted to the routine use of 60 per cent Renografin for carotid arteriography; an additional 1,500 arteriograms done with 60 per cent Renografin have been quite satisfactory."[7]

better tolerated even in pediatrics... Citing some difficulties in administering contrast agents intravenously to children, Strasser *et al.*[8] selected Renografin-60 for intramuscular use in excretion urography in 16 pediatric patients because of the mild and relatively few reactions consistently associated with its use. The authors concluded: "The almost complete absence of any kind of local effect from its injection into the gluteal muscle and the absence of any serious reactions, local or systemic, indicate the safety of the medium."[8]

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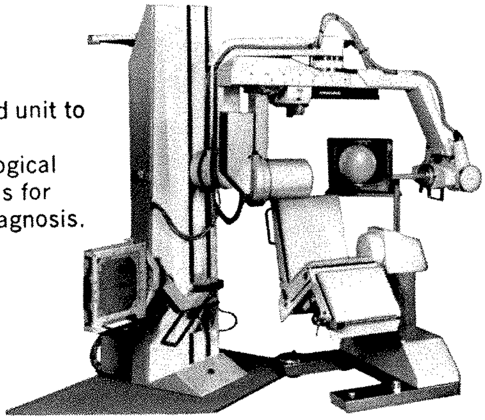

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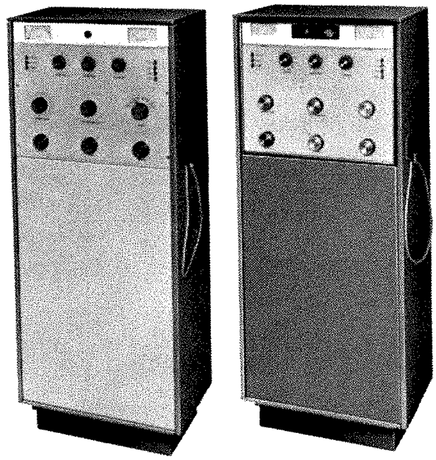

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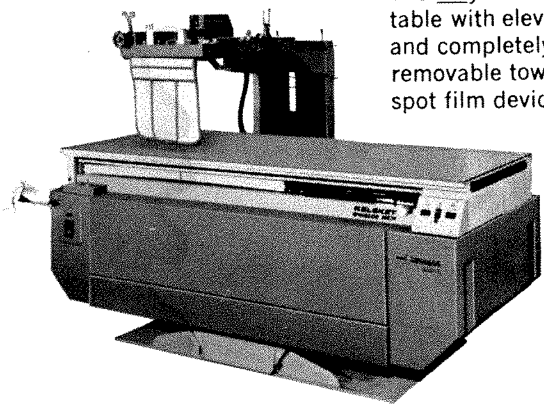

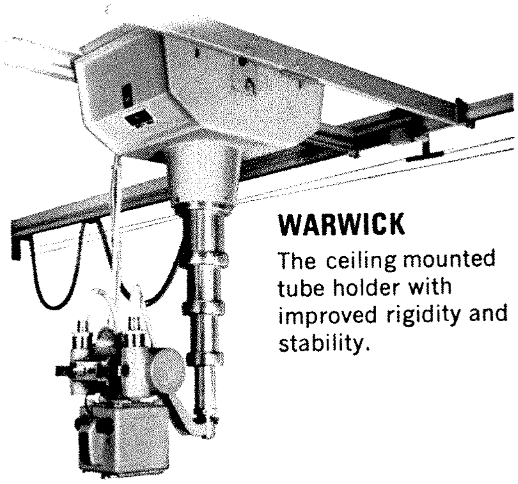

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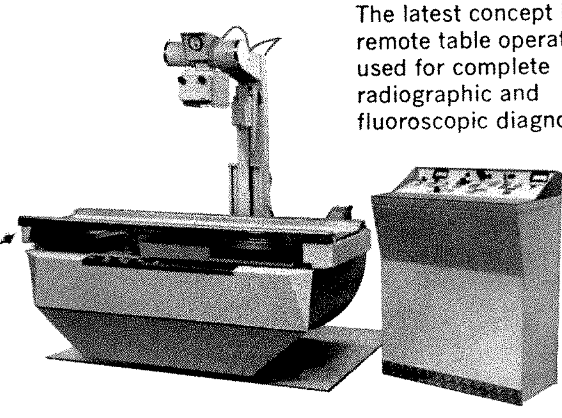

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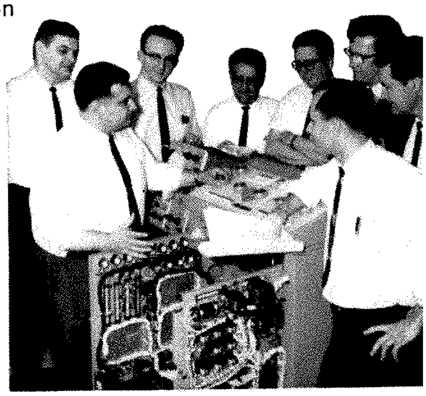

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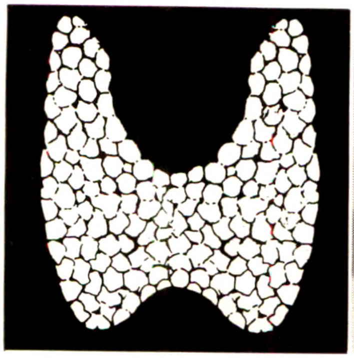
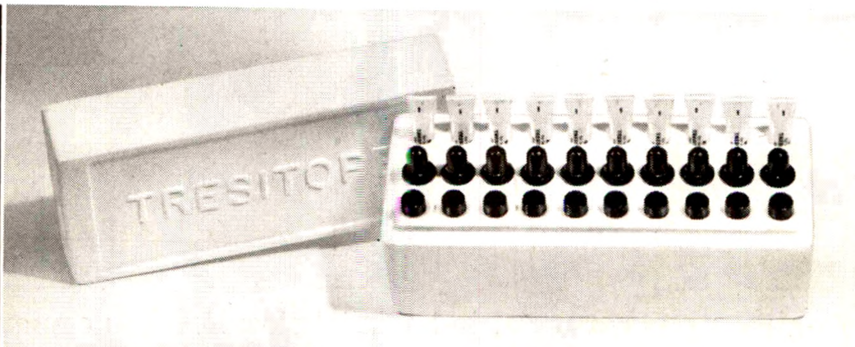
SQUIBB

a research concept in radiodiagnostics

Some significant advances in thyroid-testing technique

In the continuing research for superior thyroid function tests, the *in vitro* Tresitope procedure represents important refinements in safety and simplicity—with longer shelf life of test material.





The Tresitope Diagnostic Kit offers significant refinements in the performance of the resin uptake test for thyroid function. First, it employs I^{125} which permits a much longer shelf life of test materials than I^{131} and also lowers radiation exposure to the technician. Second, the kit is completely self-contained—no other equipment is required. And, as an *in vitro* test, it avoids exposing patients to any ionizing radiation, and the results are unaffected by the prior administration of most iodine-containing preparations. Furthermore, the technique is simple enough so that the test can be run in any hospital or office laboratory with suitable isotope facilities, and the amount of radioactivity is sufficiently small so that no AEC licensing is necessary, provided that not more than 100 vials of Liothyronine I^{125} Buffer Solution are on hand at any one time.

The technical difficulties encountered in preparing different batches of resin sponges are avoided.

Moreover, because it is an *in vitro* test, it is diagnostically significant in the presence of unrelated nonthyroidal factors that are known to complicate interpretation of other test findings. More specifically, the test is unaffected by anxiety, hypertension, congestive heart failure, or administration of mercurial agents. And it is unaffected by prior administration of most iodine-containing preparations that can completely nullify the results of other thyroid function tests for considerable periods.

I^{125} versus I^{131}

The use of I^{125} rather than I^{131} to label the liothyronine employed in the test is also advantageous. Employing I^{125} considerably lengthens the shelf life of the liothyronine because I^{125} has a longer half-life and also because it emits no beta rays to affect the stability of liothyronine. The half-life of I^{125} is considered to be 60 days while I^{131} has a half-life span of approximately 8 days. Other advantages of I^{125}-labeled material include lowered radiation exposure to the technician, yet radioactivity is well within good counting range of modern standard equipment and *in vitro* counting is quite efficient.

convenient, safe, and practical

The Tresitope Diagnostic Kit was specifically designed so that the test procedure is simplified and the possibility of radioactive contamination of the laboratory is minimized. The kit contains 10 capped vials, each containing Liothyronine I^{125} Buffer Solution (activity does not exceed 0.1 microcurie per vial), 10 plastic tubes of resin powder, and 10 separate droppers to avoid cross-contamination. The polystyrene carrier is also a test-tube rack, and it has been modified to facilitate washing of the resin powder. The reverse side of the package insert becomes the record sheet for test results.

NOTE: While the resin uptake test is a very useful aid in the evaluation of thyroid function, it should not be used as the sole basis for such an evaluation. In any patient, the clinical state is probably the best indication of thyroid status, and *any* laboratory test must be interpreted with caution when test results do not agree with clinical evidence.

Precautions

Use appropriate radiation precautions in handling, identifying and discarding all radioactive material. Remember that minute amounts of radioactivity remain on components used in the test, including the polystyrene platform when it is used in performing the test, and particularly when the Tresitope Suction Method is used for a number of tests.

Tresitope® Diagnostic Kit

Squibb Resin Uptake Kit with Liothyronine I^{125} Buffer Solution

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THE AMERICAN RADIUM SOCIETY

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Fiftieth Annual Meeting, American Radium Society
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April 7-11, 1968
For Preliminary Program see January Issue

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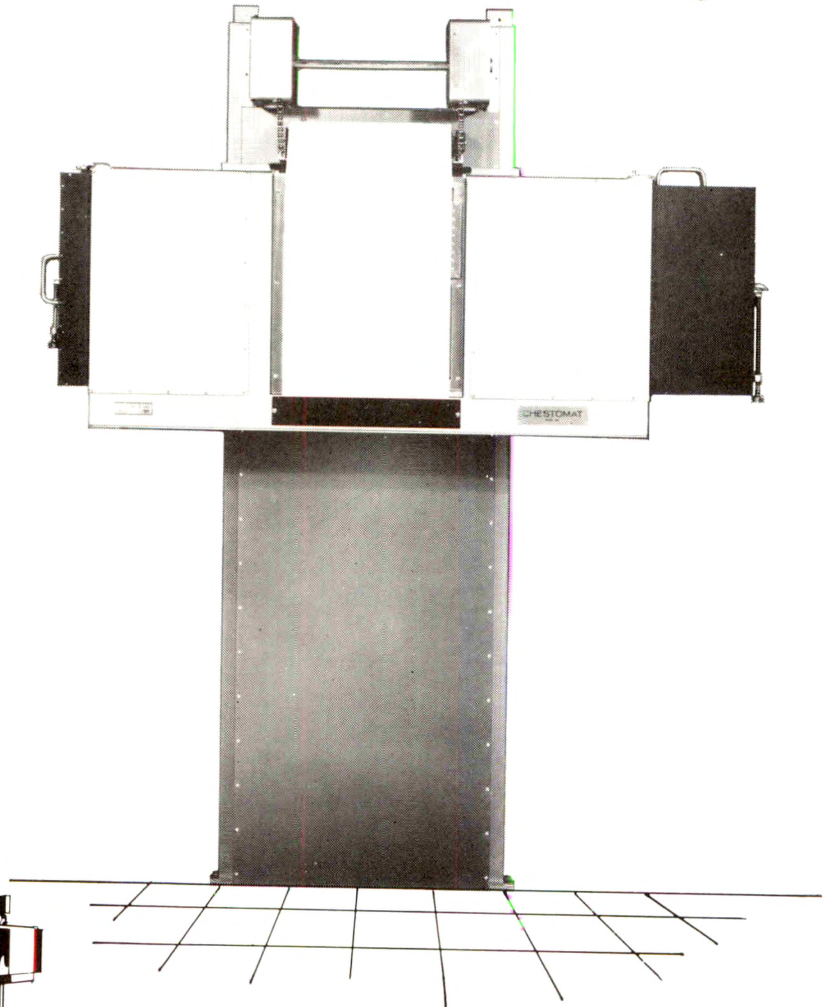
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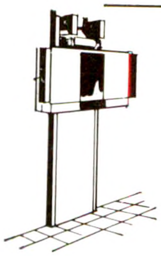

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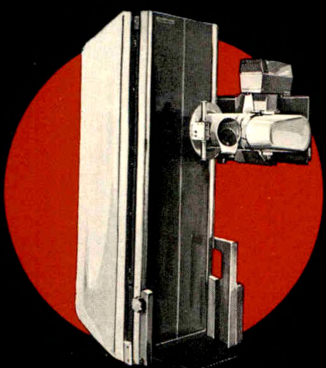

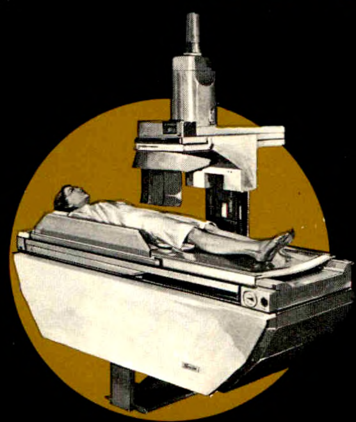

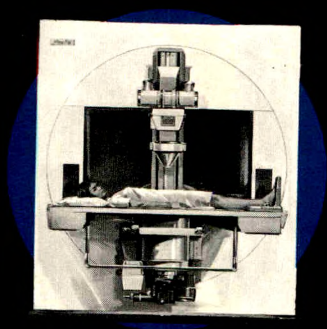

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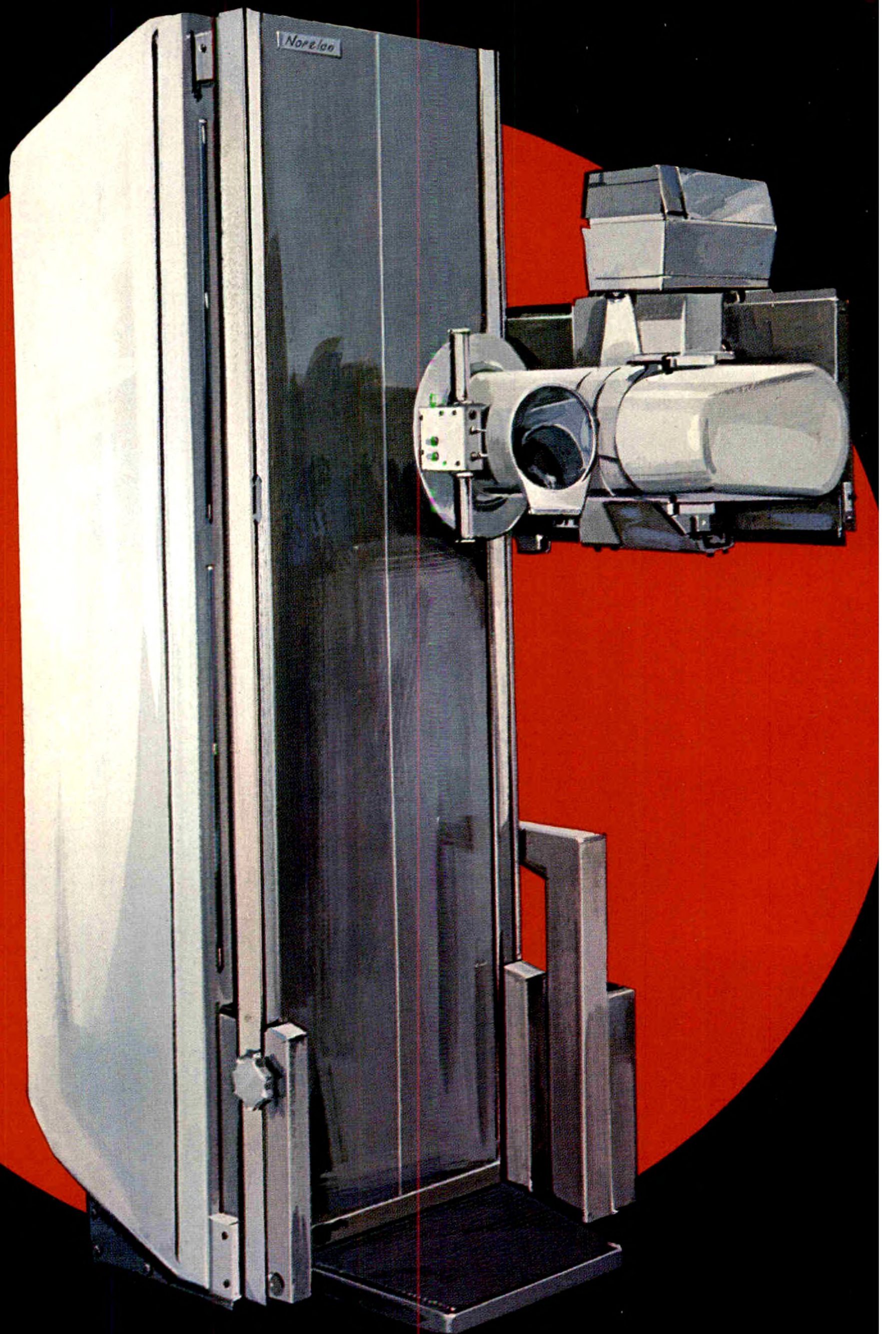
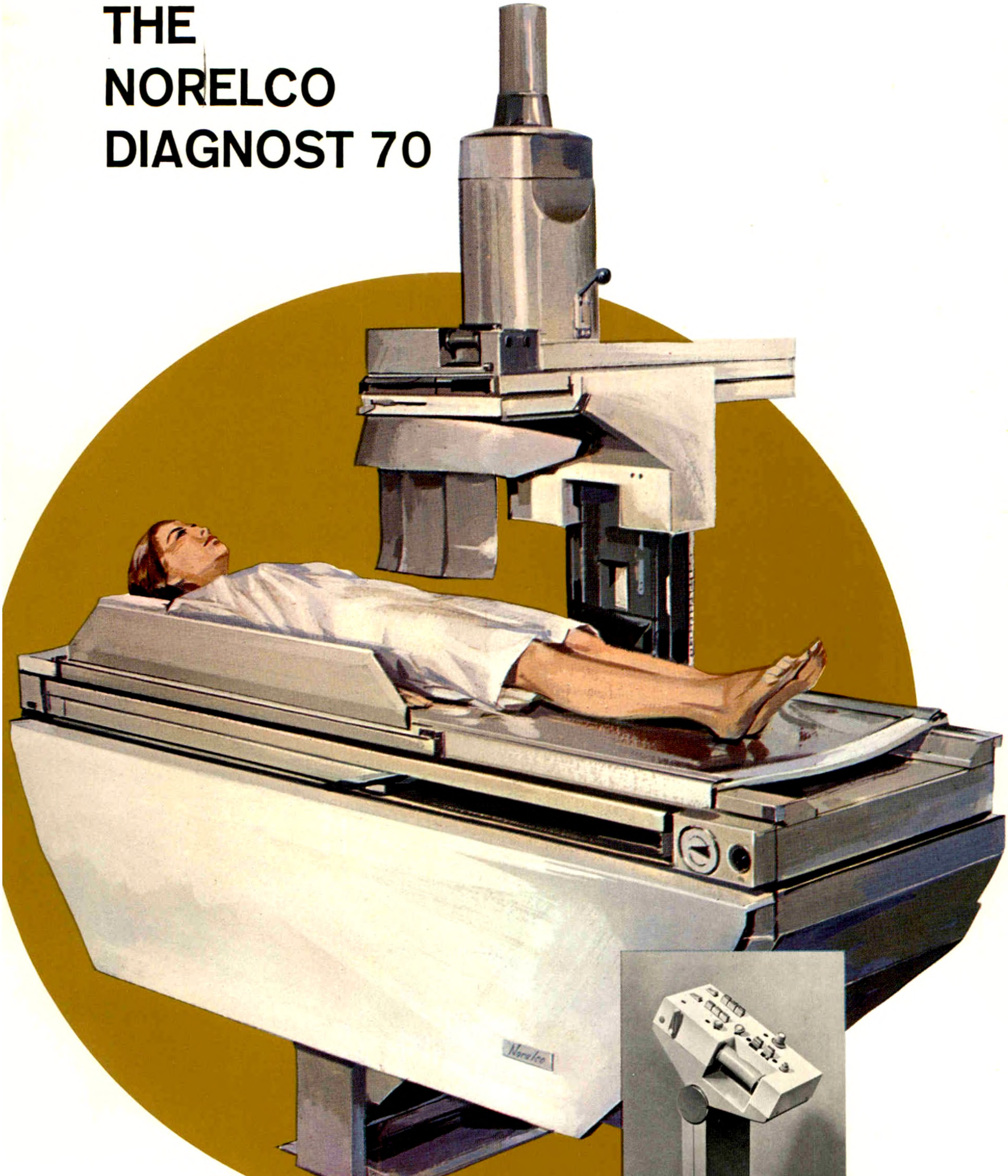


90° / 15° table with self-suspended 6″ image intensifier mounted for swing-away parking. Offering fluoroscopy with TV chain or mirror viewer and recording with 70mm spotfilm, cine, or video tape.

THE NORELCO DIAGNOST 70



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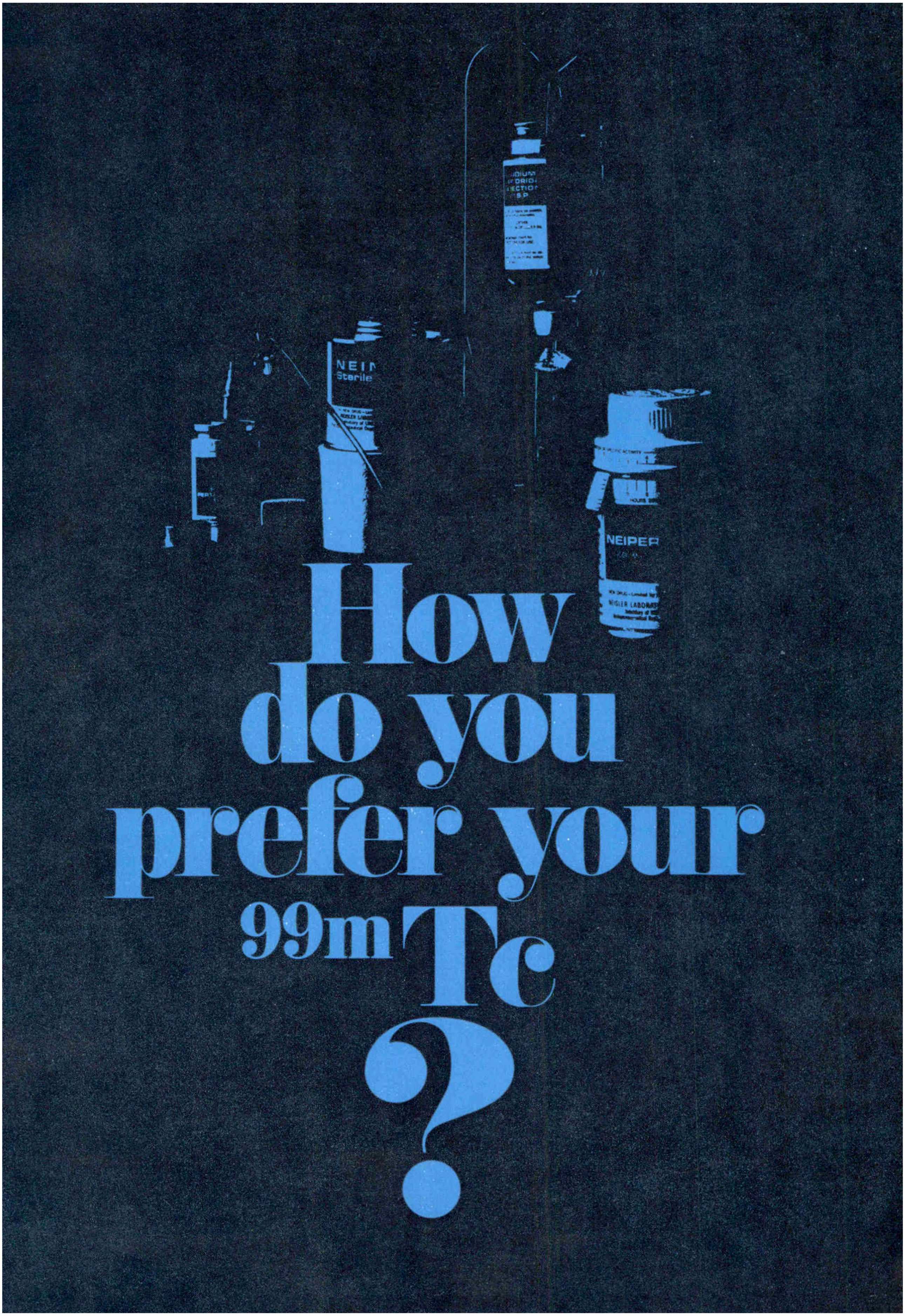
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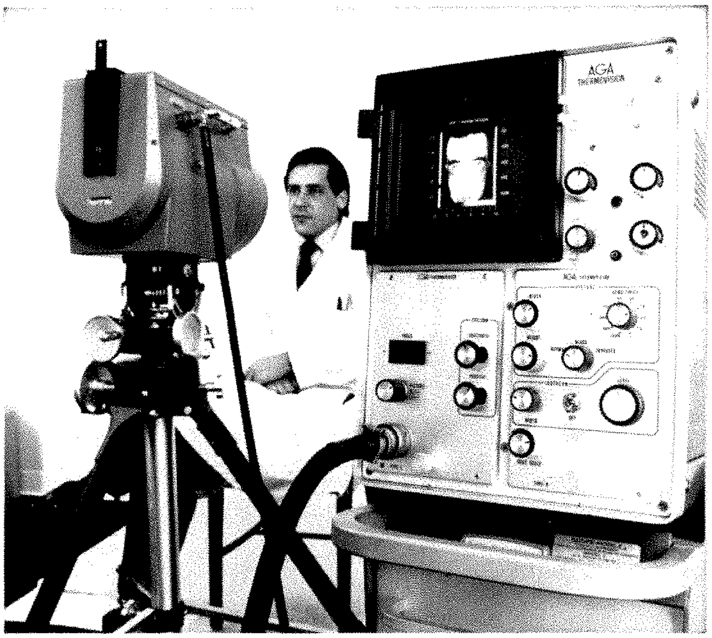

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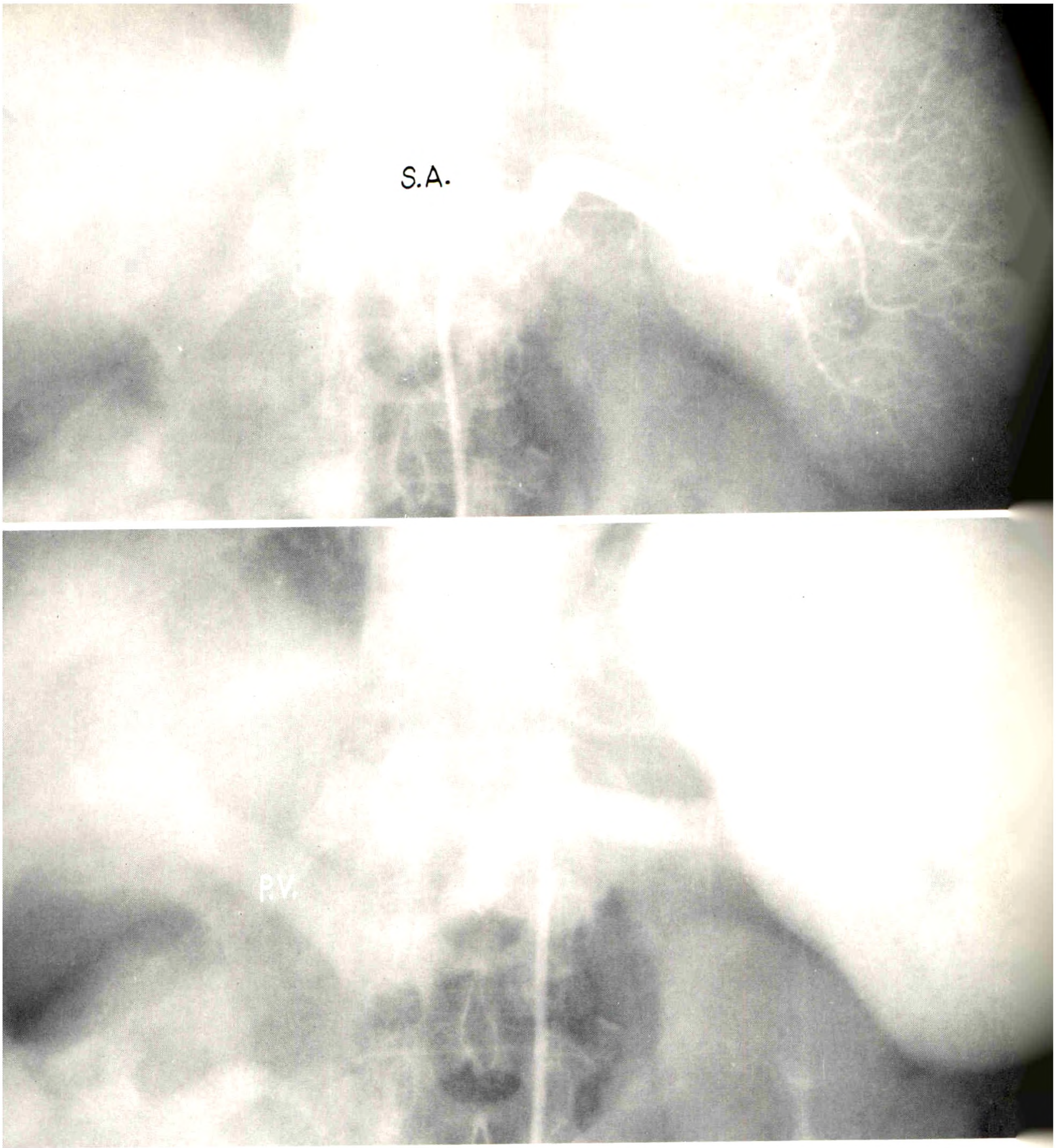

Injection factors: 60 ml of 75% Hypaque (contrast medium) at delivery rate of 10 ml/sec.
Legend: SA—splenic artery; PV—portal vein; C—collateral; SV—splenic vein.

DIAGNOSIS:

Portal hypertension

TECHNIQUE: Selective splenic arteriography

DESCRIPTION (top photo): Arterial phase (normal)

DESCRIPTION (bottom photo): Absent perfusion of liver via portal vein. Portal flow diverted through collateral.

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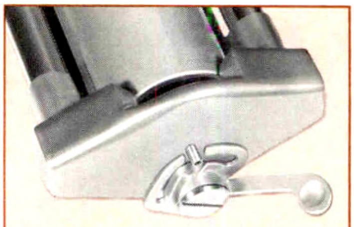

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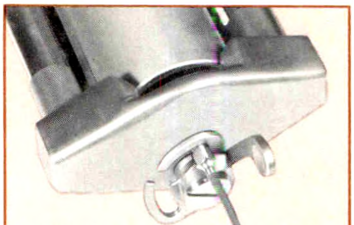
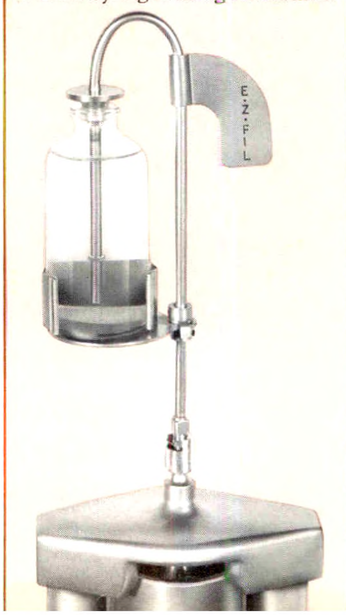


Quic-Loc: catheter connected

E-Z-Fil Syringe Filling Attachment



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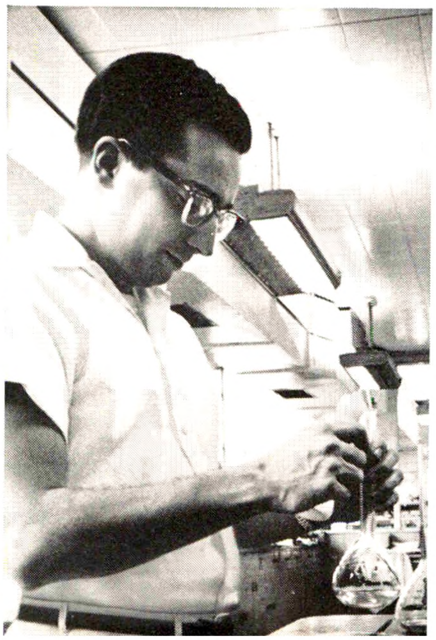

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SQUIBB

a research concept in radio pharmaceuticals

New help in diagnosing pulmonary problems

New radioisotope scanning procedure can help detect the vascular changes of pulmonary disease before they show on chest films

Scintiscanning of the lungs now offers a new approach to the diagnosis of pulmonary disease.[1] With use of macroaggregated radio-iodinated I^{131} albumin, lung scanning has been found to be simple, rapid and relatively safe,[2,3] and is invaluable as an adjunct to other diagnostic procedures whenever information about pulmonary vasculature is desired.

Perhaps the most useful application of the lung scan has been for the early detection of pulmonary embolism where "... it appears that the lung scan can point to the site of embolic lesions before signs of lung infarction are recognizable on plain chest films."[3] This is important, for with the development of new means of treating pulmonary embolism, the need for improved diagnostic ability has increased. For example, the availability of anticoagulant drugs to prevent further thrombosis and of proteolytic agents to dissolve thrombi already formed, the use of surgical therapy (such as ligation or plication of the inferior vena cava and even pulmonary embolectomy) — all require more accurate diagnostic procedures.[4,5]

Of course, pulmonary arteriography can give an immediate positive demonstration of an obstruction in the pulmonary circulation as soon as it occurs, but this procedure is time consuming and technically difficult to perform. It necessitates injection of large quantities of high density contrast medium directly into the pulmonary artery, and it also requires cardiac catheterization (with some risk of dislodgement of venous thrombi). Moreover, experience has shown that patients with pulmonary hypertension may tolerate injections of contrast material poorly. Other examinations, such as x-ray study of the chest and electrocardiography, are rarely definitive.[4]

In contrast, lung scanning with Albumotope-LS is a simple and direct adjunctive measure; reliable and virtually without risk of morbidity to the patient. And unlike pulmonary arteriography it does not require cardiac catheterization and involves only minimal inconvenience to the patient. All that is required is the i.v. administration of a relatively small amount of the isotope. And the test may be supplemented with other procedures when necessary.

Although the lung scan has been used most frequently for the detection of pulmonary emboli, it can provide useful information in the diagnosis and evaluation of other pulmonary problems. For example, a recent report[6] in the September, 1966, issue of *Circulation* discusses the potential applicability of the technique in the detection and assessment of mitral valve disease. According to the authors, the technique has been found useful in screening patients with clinical findings of mitral valve disease who were not considered symptomatic enough to warrant cardiac catheterization ... in the preoperative study of patients so ill that left heart catheterization was unusually hazardous ... and in determining whether the pulmonary venous pressure is elevated in patients with known severe pulmonary arterial hypertension. In these latter patients it is often difficult to measure pulmonary arterial wedge pressure reliably and the more extensive manipulations necessary for left heart catheterization may be poorly tolerated. Thus, assessment of the distribution of pulmonary arterial blood flow by lung scanning affords a means for determining the existence of pulmonary venous hypertension, which suggests the presence of potentially correctable lesions, such as mitral stenosis or cor triatriatum.[6]

Photoscan of lungs of female patient, aged 50, showing pulmonary emboli. Chest x-ray taken same day showed no radiographic evidence of pulmonary embolism.*

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Squibb Aggregated Radio-Iodinated (I^{131}) Albumin (Human)

References:
(1) Quinn, J. L., III; Whitley, J. E.; Hudspeth, A. S., and Prichard, R. W.: Radiology *82*:315 (Feb.) 1964. (2) Sabiston, D. C., Jr., and Wagner, H. N., Jr.: Ann. Surg. *160*:575 (Oct.) 1964. (3) Haynie, T. P.; Hendrick, C. K., and Schreiber, M. H.: J. Nucl. Med. *6*:613, 1965. (4) Wagner, H. N., Jr., *et al.*: New Eng. J. Med. *271*:377 (Aug. 20) 1964. (5) Quinn, J. L., III; Whitley, J. E.; Hudspeth, A. S., and Watts, F. C.: J. Nucl. Med. *5*:1 (Jan.) 1964. (6) Friedman, W. F., and Braunwald, E.: Circulation *34*:363 (Sept.) 1966.

Dosage and Scanning Procedure: Recommended scan doses of 150 to 300 microcuries of aggregated radioiodinated (I^{131}) albumin depending on the instrumentation available and the technics employed. Scanning immediately follows administration of slow intravenous injection. Patient may be placed in a prone or supine position.

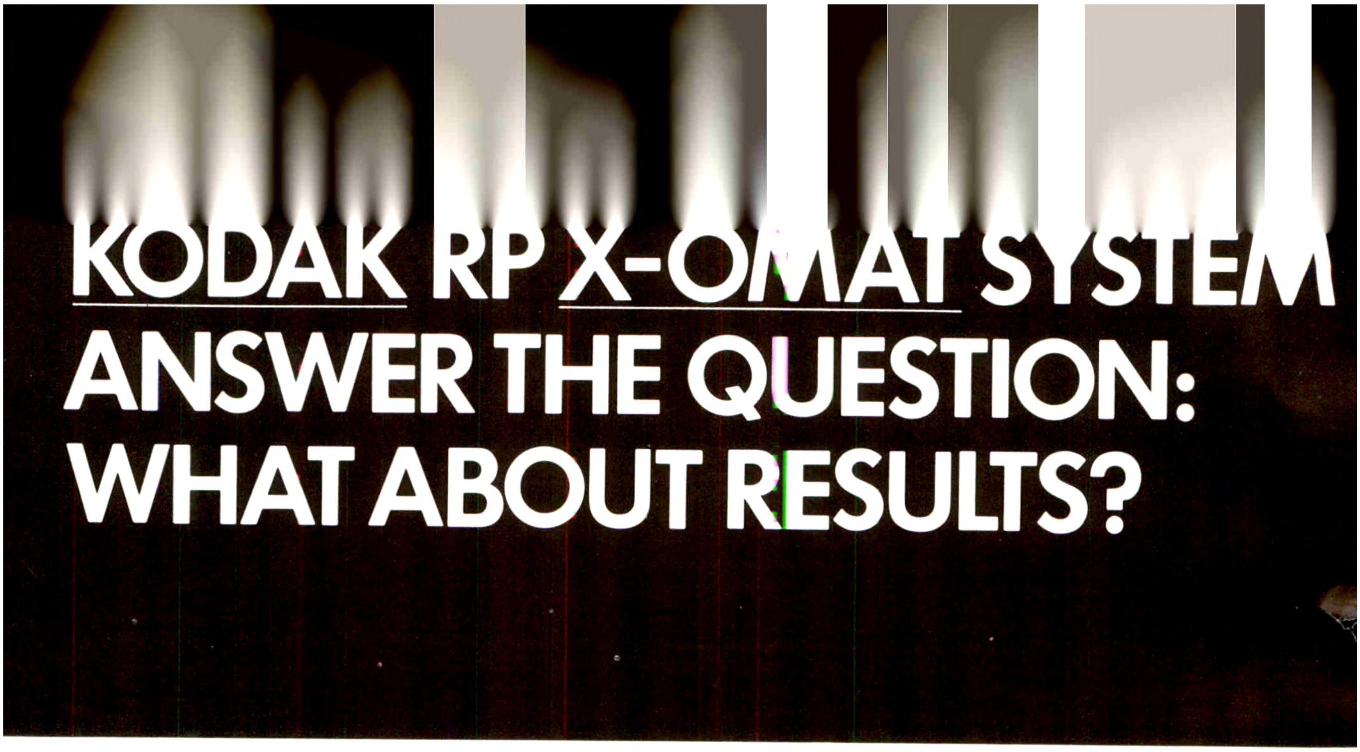
Side Effects and Precautions: Radioisotopes should not be used in pregnant women, nursing mothers, or in patients under 18 years of age unless indications are very exceptional.

There have been no reported cardiovascular or other untoward effects attributable to Albumotope-LS. Extensive clinical use of Albumotope-LS has not borne out the hypothetical possibility that particles of large size might induce deleterious cardiovascular or cerebrovascular effects. The product appears to possess no antigenic properties. One patient with a known history of angioneurotic edema, who had been given Lugol's solution in conjunction with aggregated radioalbumin similar to Albumotope-LS, developed urticaria.

Available: As a sterile, non-pyrogenic, aqueous suspension. Each cc. contains approximately 1 mg. aggregated human serum albumin labeled with 800-1500 microcuries of iodine-131 at time of manufacture. Also contains 0.9% benzyl alcohol as a preservative.

*Illustration furnished through the courtesy of George V. Taplin, M.D., Harbor General Hospital, Torrance, California.

SQUIBB 'The Priceless Ingredient' of every product is the honor and integrity of its maker.



KODAK RP X-OMAT SYSTEM ANSWER THE QUESTION: WHAT ABOUT RESULTS?

When Kodak introduced its 90-second processing system two years ago, radiologists accepted it as a great step forward. Most felt that time and careful evaluation would be necessary to reveal fully its benefits. First they wanted to know how results would compare to the conventional automatic processing they were using, then how such a system would benefit their office and hospital practices.

There have been millions of exposures now using the Kodak 90-second film and processing system. Radiologists have reported that by using integrated Kodak film, chemicals, and processors, they have been consistently achieving radiographs of highest diagnostic reliability.

How do they compare?

An objective study of the *Kodak RP X-Omat* System (Kodak 90-second film, processors, and chemicals) was recently made and published by a group of radiologists. Four hundred and forty-four films were given to radiologists for comparison—222 studies on *Kodak RP X-Omat* Film, and a total of 222 studies on two other films, each of a type requiring longer processing times. All film identification markings were obscured with black masking tape. This is the conclusion reached by the radiologist-authors: "Gross visual characteristics of the RP and standard film are equal; RP Film detected anatomic detail, both normal and abnormal, as well as the standard film and made possible the same radiologic diagnosis."[1]

1. As published in the September, 1967, JOURNAL OF THE CANADIAN ASSOCIATION OF RADIOLOGISTS, Vol. XVIII, pages 389-392. For your copy of the full report, write: Eastman Kodak Company, Radiography Markets Division, Rochester, N.Y. 14650, or contact your Kodak Technical Sales Representative.

Three Kodak 90-second films

Further, Kodak offers radiologists a choice of three 90-second films, each with different characteristics. Any one might suit a particular radiologist's practice, or a combination of two or even three might give desired results. All three—Kodak RP, RP/S, and RP/L—produce radiographs of traditional Kodak quality and uniformity. To select the one film or combination of films best suited for your practice, ask your Kodak Technical Sales Representative to demonstrate each film. By seeing the distinct characteristics of each, you will be able to choose which film or combination of films is best for you.

You can't beat the system

The full control you achieve because of the quality and choice of three Kodak 90-second films in a variety of radiographic situations is augmented by the nature of the *Kodak RP X-Omat* System. Its components—film, processor, and chemicals—are designed to work together, engineered to be easily and accurately maintained, providing uniform results. By working with the system, radiologists and technologists know what they're working with and what they can expect. Instead of variance, there's uniformity. Instead of disappointments, there are predictable, quality results, time after time.

How efficient is the system?

"The Kodak 90-second processing system is nearly five times faster, but do I need it?" you might ask. That's a matter for individual consideration. Yet early studies and reports from those now using the system show what it can do. Kodak 90-second processing, according to one such study, means the capability to handle a work-load increase of 18 percent. By utilizing 90-second *dispersed* processing (an *RP X-Omat* Processor for each two examination rooms), even greater benefits can be attained. Dispersed processing can reduce examination-room occupancy, on the average, by up to 25

percent. That means case load may be increased by 31 percent over that possible with 7-minute central processing.

What does it mean in practice?

Reports from radiologists now using the Kodak 90-second processing system translate these figures into very real benefits. To the radiologist, it means increased utilization of examination room and equipment, handling more patients with no expansion of facilities or staff. It means significant speeding up of fluoroscopic and other serial examinations that require processed films during the course of the examination. It means improved flow of "doctor-ready" patients.

Increased patient comfort

The patient benefits by the greater efficiency of the radiological team in terms of better care—particularly in hard-pressed facilities. Nearly immediate delivery of processed films means greater patient comfort through shortened serial examinations, elimination of patient call-backs. Radiologists also report that treatment can often be started sooner. Further, many radiologists report that anesthesia time during special procedures can be materially reduced.

Hospitals, technologists gain, too

Kodak 90-second processing means greater economy through greater efficiency for both hospital and private office practices. Examination facilities that seem to shrink day by day under increasing case loads can do the job without further expansion.

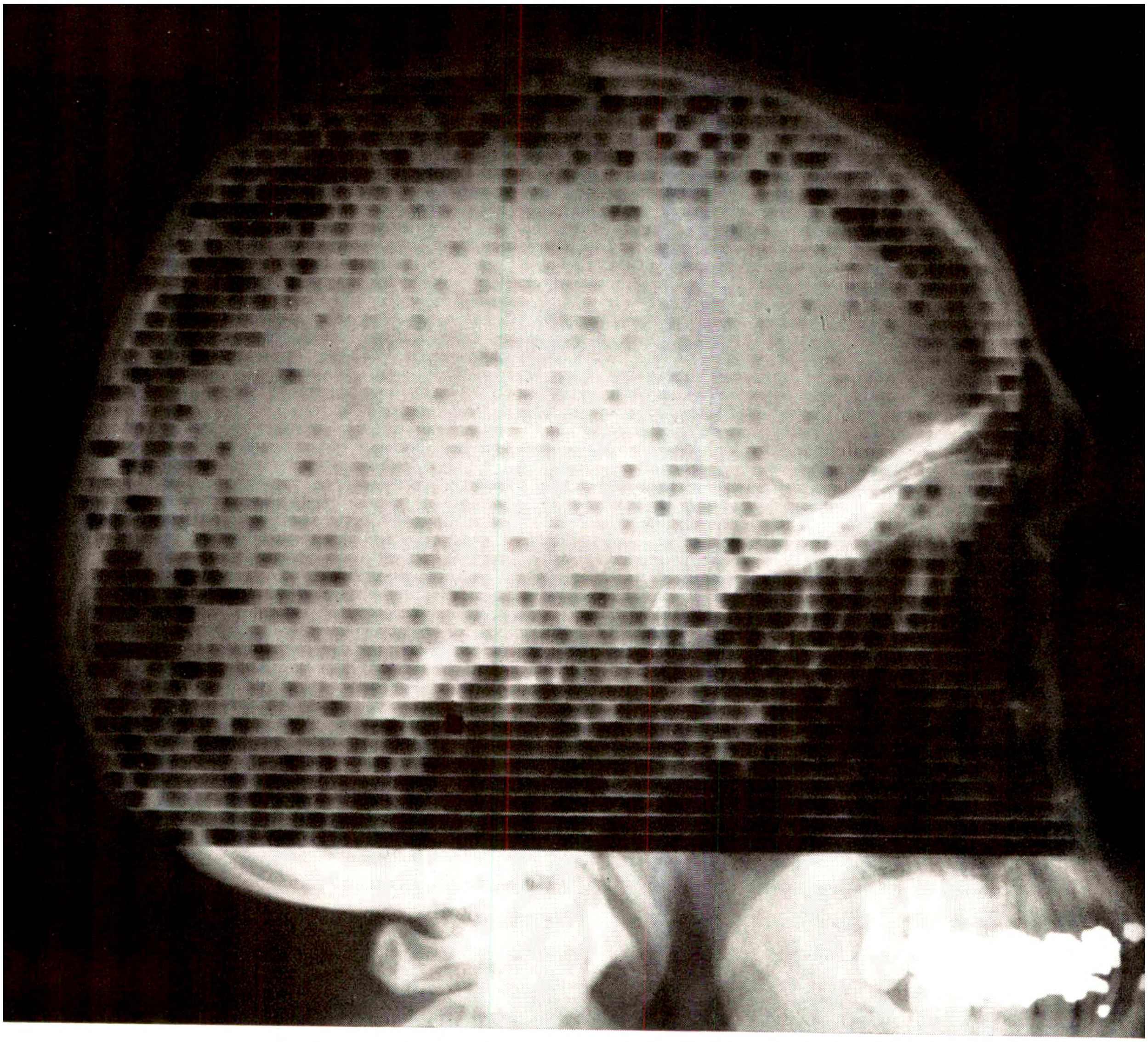
The technologist becomes more efficient working with the Kodak 90-second processing system. Immediate film access reduces film loss or misplacement. Quality improves because technic can be checked before the patient leaves the room; finished radiographs can be correlated with the technic used. There's no time loss and confusion from a processing backlog. Only 6½ minutes are required to process a 20-film series of 14 x 14-inch radiographs in a *Kodak RP X-Omat* Processor, Model M6.

EASTMAN KODAK COMPANY
Radiography Markets Division
Rochester, N. Y. 14650

Updating is easy

Moving up to the Kodak 90-second processing system requires no real re-orientation or new skills. Technic is the same . . . processing is done five times faster. For new installations, the *Kodak RP X-Omat* Processor, Model M6, is compact, durable, trouble-free. It takes less than 5 square feet of floor space and is ideally suited to dispersed processing—in many cases without structural changes.

Your Kodak Technical Sales Representative will be happy to give you full details as to how the Kodak 90-second processing system works, why its components were specially designed to work together, and how you might best take advantage of this revolutionary new system. Get in touch with him or your *Kodak X-Omat* Dealer for full details.



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INDICATIONS: Adjunctive diagnostic aid in detecting and localizing intracranial neoplastic (primary or metastatic) and non-neoplastic lesions.

CONTRAINDICATION: Radio-pharmaceutical agents should not be administered to pregnant women or to persons less than 18 years old unless the indications are very exceptional.

PRECAUTIONS: Care should be taken to ensure minimum radiation exposure to the patient as well as all personnel; to prevent extracranial contamination because this can lead to erroneous interpretation; and to differentiate areas of abnormal activity from areas of normal vascular activity.

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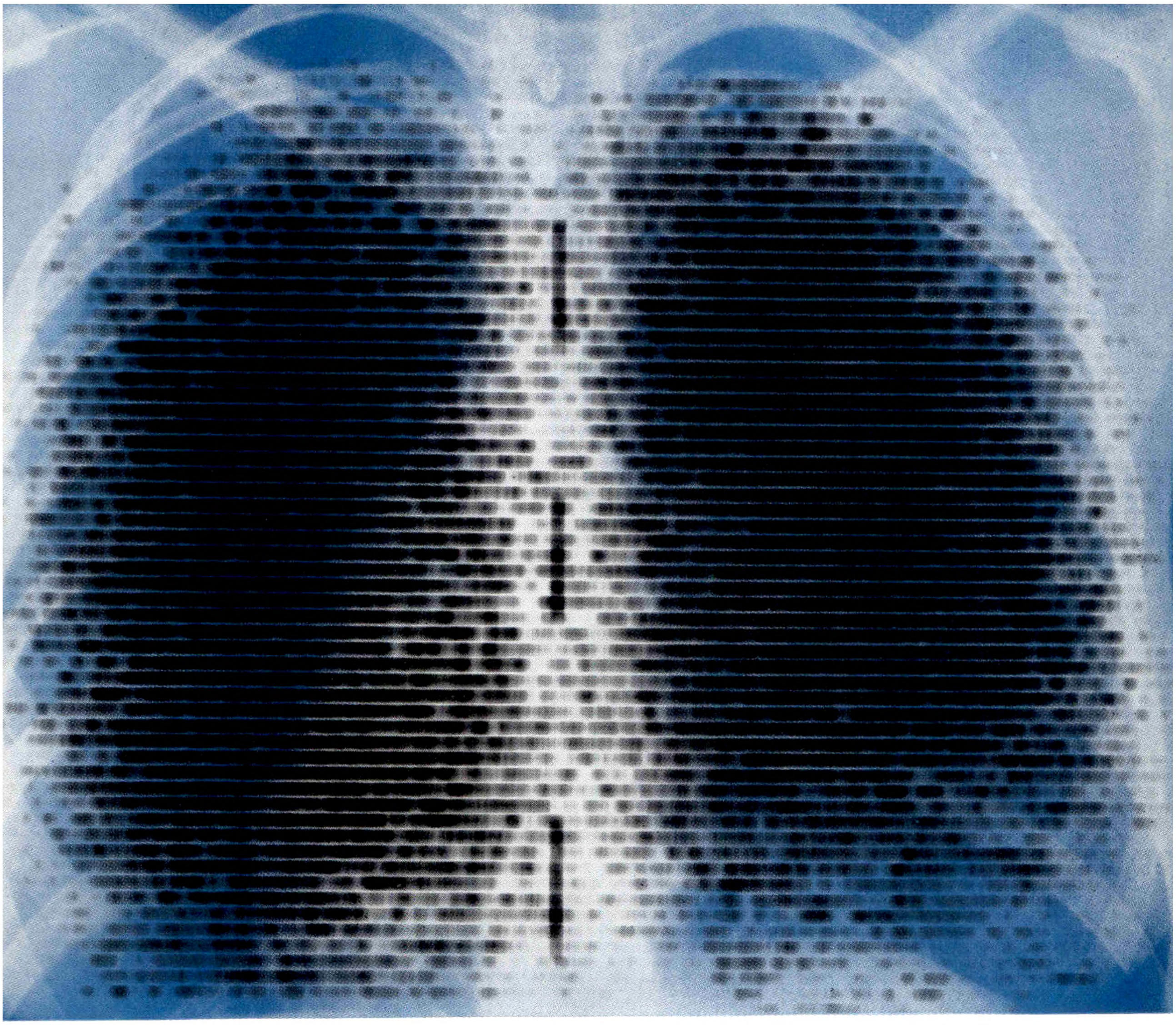

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Lung tumors: To evaluate the regional ischemia resulting from compression or obstruction of pulmonary arteries.

Surgery and/or other therapy for lung disorders: To evaluate the effectiveness of therapeutic measures.

Macroscan-131 is sterile and non-pyrogenic. It is ready to use and should not be heated prior to use.

INDICATIONS: For scintillation scanning of the lungs to evaluate total, unilateral, and regional arterial perfusion to the lungs.

CONTRAINDICATION: Radio-pharmaceutical agents should not be administered to pregnant women, nursing mothers, or to persons less than 18 years old unless the indications are very exceptional.

PRECAUTIONS, SIDE EFFECTS: Care should be taken to administer the minimum dose consistent with safety and validity of data. The possibility of an immunological response to albumin should be kept in mind when serial scans are performed. There is a theoretical hazard in acute cor pulmonale, because of the temporary small additional mechanical impediment to pulmonary blood flow. A possible case of urticara has been related to a similar preparation. The thyroid gland should be protected by prophylactic administration of concentrated iodide solution.

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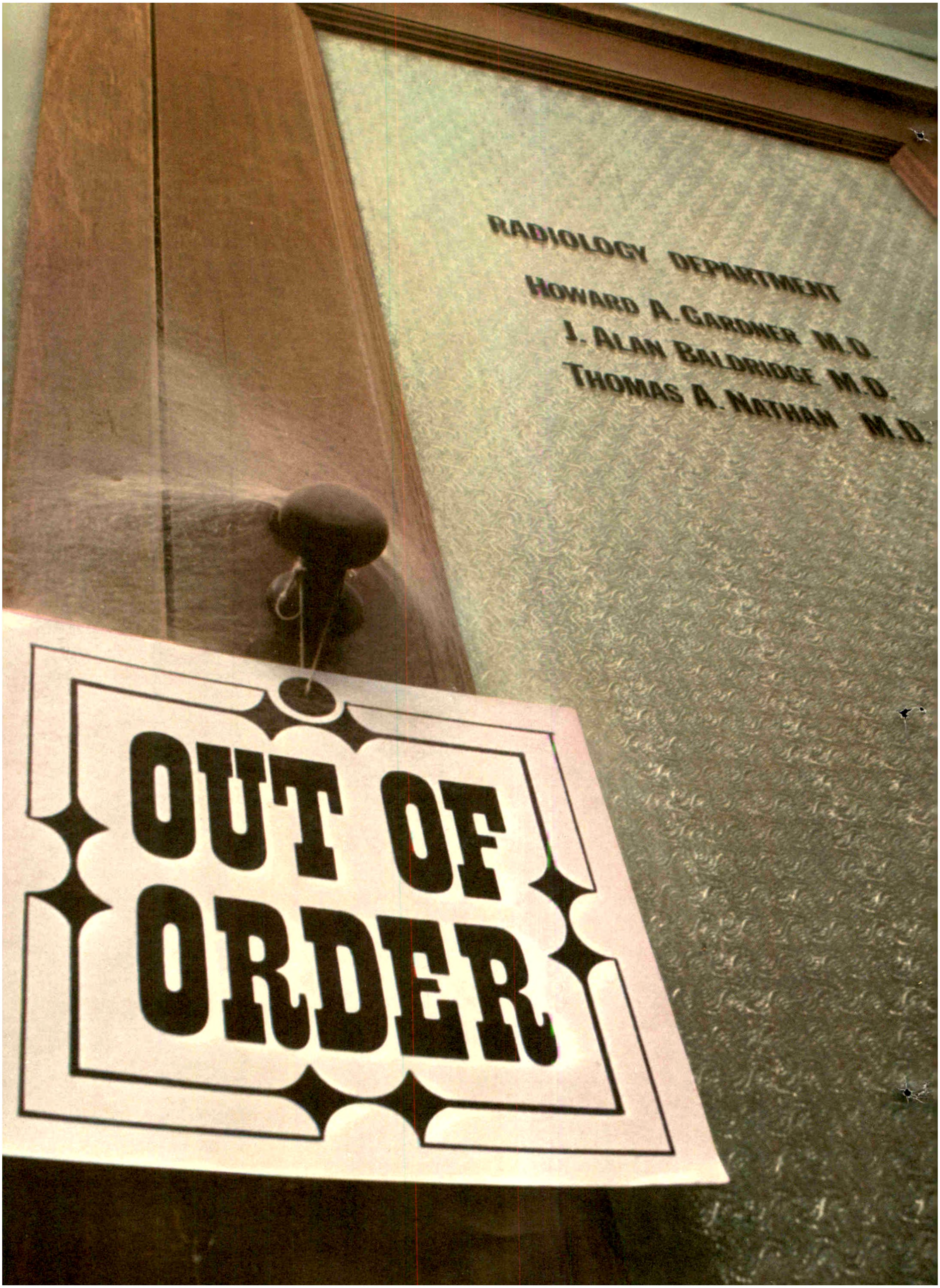
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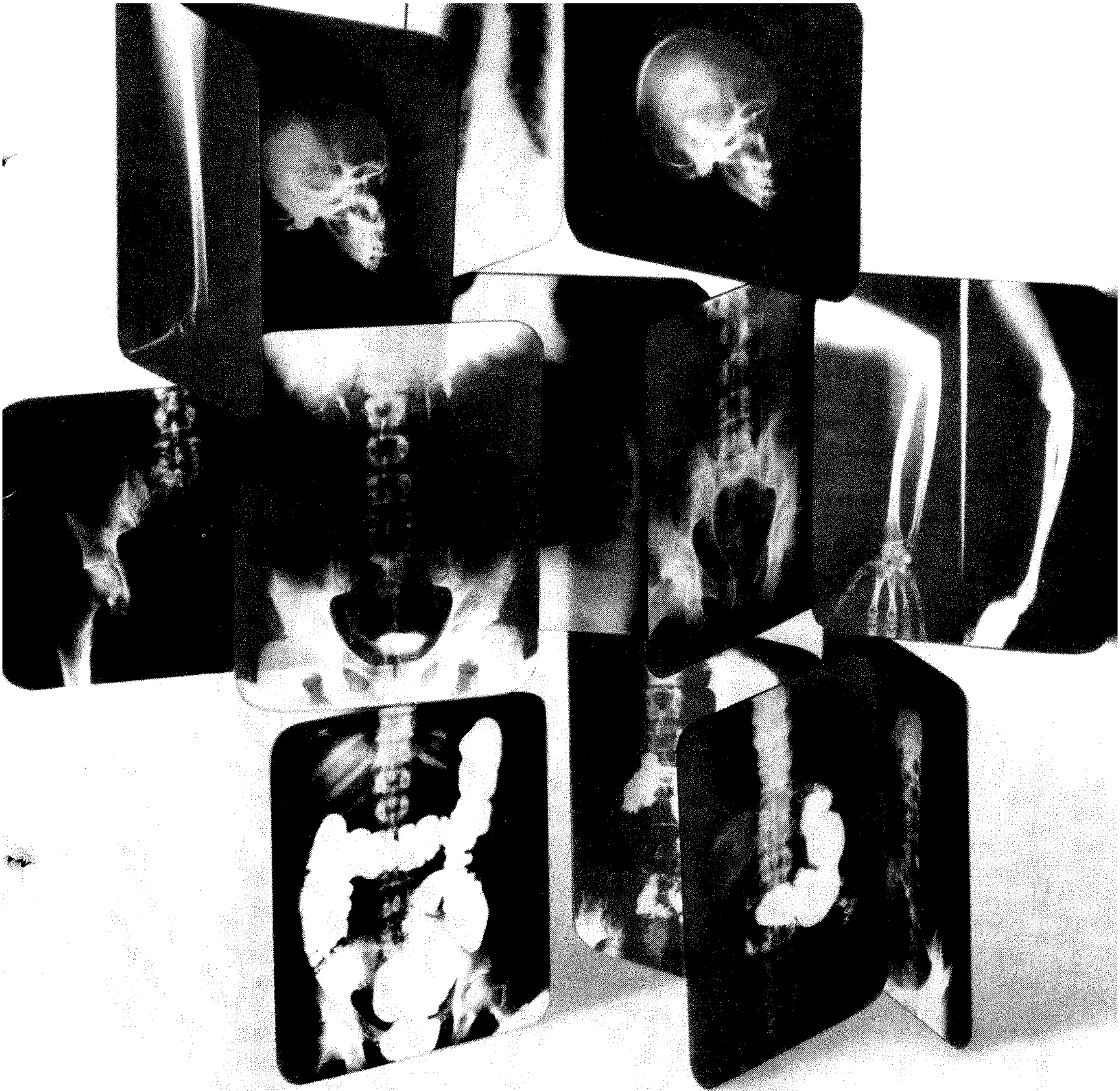

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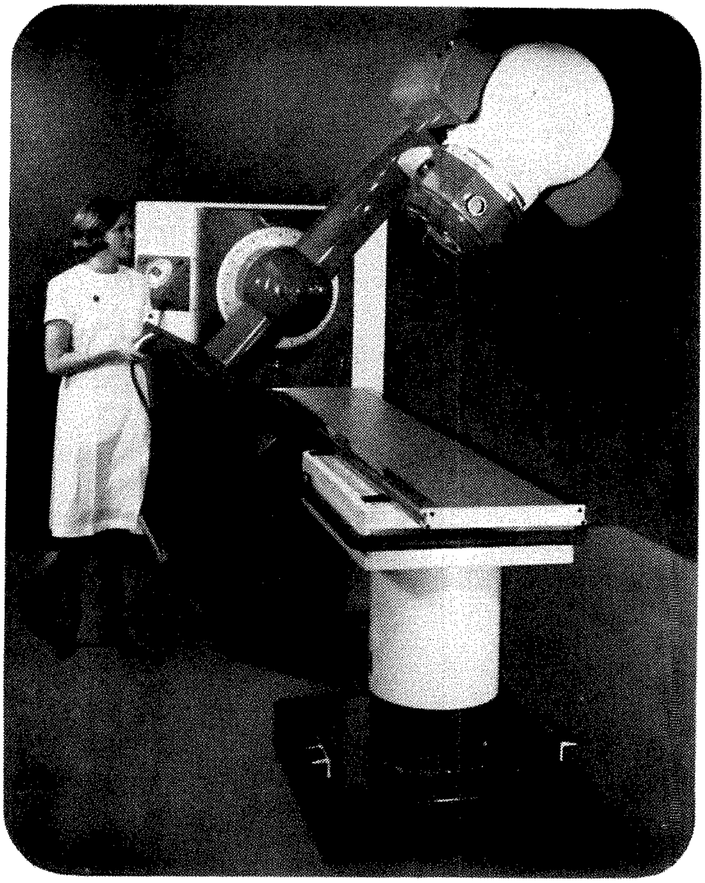

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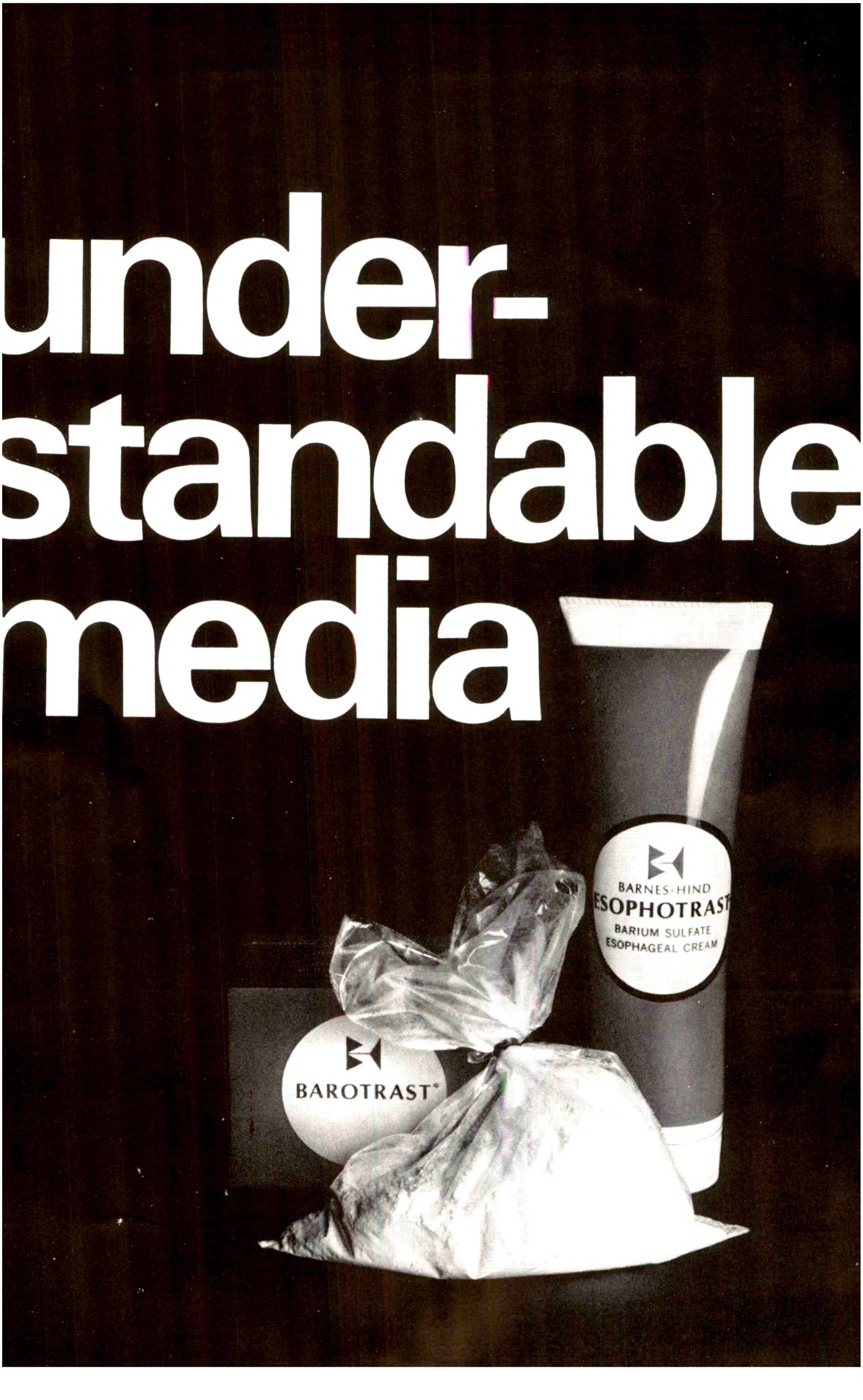
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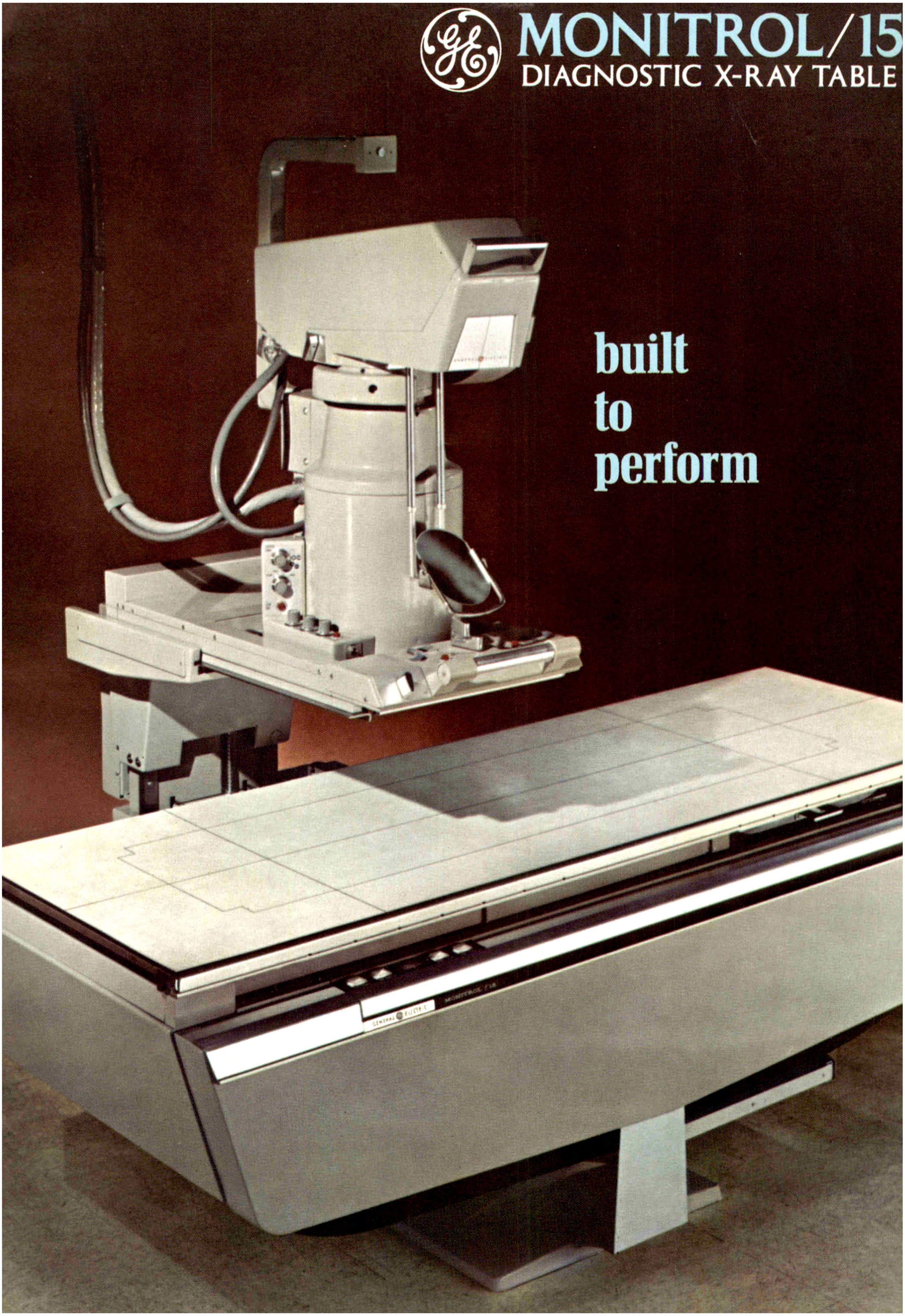
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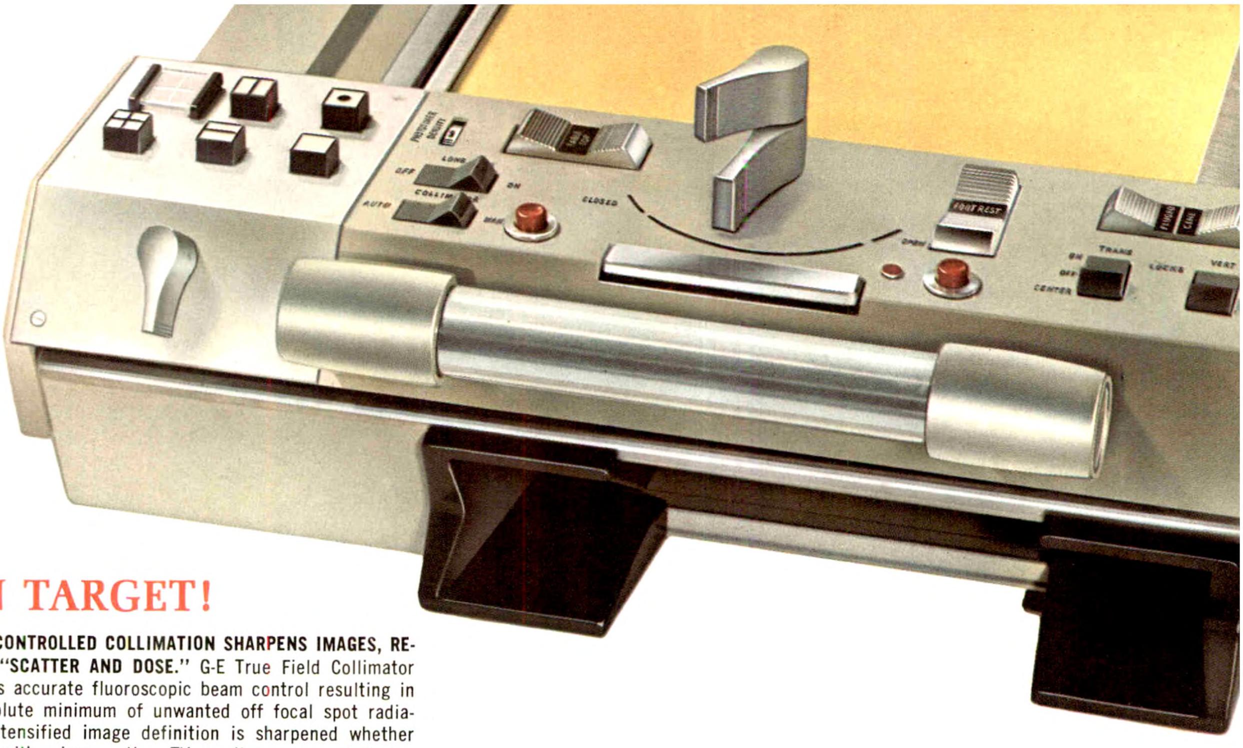

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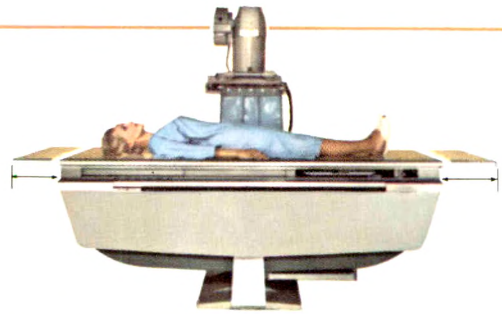
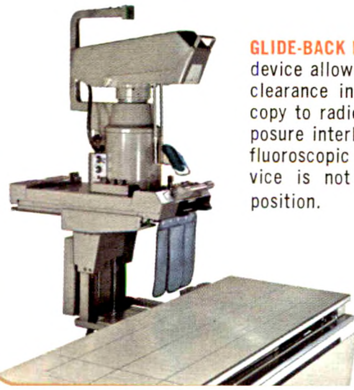


POWER-DRIVEN GLIDE-TOP speeds procedures. A choice of table head-and-foot travel, 30-inch head/30-inch foot or alternate 45-inch head/45-inch foot is made at installation.



GLIDE-BACK PARKING of spot film device allows for rapid table top clearance in shift from fluoroscopy to radiography. Parking exposure interlock switch prevents fluoroscopic exposure when device is not locked in forward position.

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R. LEE CLARK, M.D.
Janeway Lecturer, 1967

THE AMERICAN JOURNAL OF ROENTGENOLOGY RADIUM THERAPY AND NUCLEAR MEDICINE

VOL. 102 | MARCH, 1968 | No. 3

SYSTEMIC CANCER: PHILOSOPHY AND MODALITIES OF TREATMENT*

THE JANEWAY LECTURE, 1967

By R. LEE CLARK, M.D.†

HOUSTON, TEXAS

IN 1900 there was essentially no recorded cure rate for any but the most superficial of cancers. Today we are realizing only a 35± per cent over-all cure rate in cancer (*viz.*, no evidence of disease 5 years post therapy). Yet in this spectacular century that began with man traversing his continent in a horse-drawn wagon and, in the comparatively short span of 60 years, has sending him hurtling through space to explore the route to the moon, why have we not realized similar progress in the conquest of a disease that predates the invention of the wheel?

Who are these 35 per cent, and who the ill-fated 65 per cent? Perhaps the simplest explanation is that the 35 per cent are comprised of people with one kind of cancer—localized—and the 65 per cent of people with another—systemic or generalized cancer. Imaginative and dynamic advances have been made in the diagnosis and treatment of cancer but they have been concentrated toward efforts to inch up—per cent by per cent—this population of the 35 per cent so-called "cured of their cancer" people. I am not suggesting that these are ignoble efforts unworthy of plaudits, for they are live and exciting testimony to heroic medical feats and an impressive fount of extensive information and knowledge in and of the natural history of this disease. What I am suggesting is that perhaps our direction has been heavily biased in favor of this one group of cancer patients, to the neglect of the forgotten 65 per cent, to some of whom we give no more than our sympathy and disparagement.

Interplanetary space travel moved from an era of Buck Rogers fantasy to the world of 1967 fact—from hypothesis to realization—but not without surmounting the insurmountable. In medical science we are now at the time and place where we must launch a similar all-out assault on the seemingly insurmountable problem of systemic cancer for the benefit of those two-thirds of our patients not now being cured of their disease with present methods.

As is true with any disease the best solu-

* Presented at the Forty-ninth Annual Meeting of the American Radium Society, Toronto, Ontario, Canada, May 29–31, 1967.

† Director and Surgeon-in-Chief, and Professor of Surgery, The University of Texas M. D. Anderson Hospital and Tumor Institute at Houston, Houston, Texas.

tion to the problem of systemic cancer lies in its prevention. Too frequently definitive diagnosis is delayed through the prescribing symptomatically by the busy physician without suspicion of the underlying cause. Too often inadequate attempts are made, either by surgery or radiation therapy, to eradicate the cancer while it is still local, resulting in treatment failure which causes further delay so that when local reactivation occurs it is already associated with systemic spread.

Cancer either begins or terminates as a systemic disease. To eliminate all cancer we must develop a specific treatment method for systemic cancer through the creation of a defense mechanism in the body which either would prevent the actual development of the cancer process or would control or destroy the disease once it has become manifest.

We are now treating the cancer patient with such methods as surgery or radiation therapy aimed at eradication of the local nidus and immediately adjacent spread of the disease. We cure one-third of those patients whose cancers can be circumscribed and eliminated by these techniques. We do not cure the remaining two-thirds of our patients because either their cancers have spread beyond the confines of applicability of these techniques or, for one cause or another, the initial treatment is ineffectual allowing the cancer to reassert itself in the area of origin.

Theoretically, our cure rate can be increased to perhaps one-half of the patients instead of one-third using present treatment methods. This is predicated on more widespread application of better methods of detection and diagnosis; earlier, more effective *initial* treatment to decrease the incidence of recurrences; and lifelong follow-up of all treated cancer patients to ensure earlier detection of either recurrence or new cancers. This increase in cures from one-third to one-half can be done *only* through recognition of the need for cancer treatment by a group of physicians especially trained in this field of medicine who approach the solution as a team of experts capable of selecting the best therapy or combination of therapies for the individual patient.

What about the two-thirds of cancer patients we are not curing who die of their disease? Even if all cancer patients were treated in the earliest stage of their disease by the most versatile and knowledgeable group of cancer specialists we could not hope to save more than half of them with the means now available. The nature of the disease precludes a cure by purely local therapy because death is caused by a systemic or generalized cancer.

The past contributions of the individual entrepreneur to the advancement of knowledge in cancer treatment have been commendable. But today continued progress lies in the enlistment of the best possible elements of multiple disciplines applied to the patient in collaborative team therapy.

The treatment of cancer by an approach to its systemic nature has been going on only during the past 20 years, even though Galen undoubtedly was striving for a similar solution with his attempts to change the "bad humours" by altering the "black bile" he theorized was the seat of cancer origin.[11] In recent years we have been able to retard momentarily the progress of a generalized cancer process or reverse the dominance of a systemic cancer manifestation temporarily by altering the hormonal milieu of the patient or by administering cytotoxic drugs.

The final resolution of this problem will be attained only through the prevention or control of either the alteration in cancer cell reproduction or the lack of maturation in its progeny. All possible avenues in research investigation leading to an absolute elucidation of the intricacies of the cancer cell and its relation to the host organism must be explored.

MECHANISMS OF METASTASIS

HISTORICAL EVOLUTION IN THE UNDERSTANDING OF METASTASIS

Philip Rubin[7] concluded in a recent comment on the concept of metastases that

"There is much to be learned about the dynamics of metastasis formation, for the solution to the cancer problem lies not so much in the control of the primary, but in the ability to prevent metastases." Herein lies the crux of my argument that some of our scientific emphasis must be shifted toward an understanding of metastases and our clinical emphasis on better management of the patient.

The science of medicine has given rise to an astounding multitude of sophisticated but finite disciplines, each one of which subscribes to a theory about cancer causation unique to its discipline. Within the limited horizon of a single discipline, this unique thesis may appear overwhelmingly true to its disciples. With an intense loyalty one attributes cancer to the viral theory; another clings to abnormal differentiation; a third, that cancer represents somatic mutation. To others it is an immunologic disorder, or a self-perpetuating defect in oxidative metabolism, or an adaptive deletion of a cell component.[3] Who is right—or is it all of these? This is where we stand today in our concept of cancer and its metastatic capability.

The spread of cancer from a local focus—but not in the modern day concept of cancer cell transport to remote sites—was recognized as early as 520 B.C. when Herodotus first described local and invasive spread of cancer. Hippocrates in the fourth century B.C. classified tumors as malignant if they spread, benign if they didn't. Celsus in the early A.D. decades was advising excision of breast tumors, stressing the involvement of the axillary nodes. At the same time Galen, advancing his humoral theories, was indicting black bile as the culprit in cancer—where black bile gravitated there cancer appeared and to prevent it he advocated suppression of hemorrhoidal and menstrual bleeding.[11]

Galen's humoral thesis held sway for approximately 1500 years. From the 14th century up through the Renaissance there emerged advocates of total excision with inclusion of node dissection in cancer of the breast who recognized extension of cancer, but not metastasis *per se*. Guy de Chauliac in the 14th century removed the total disease, including what he referred to as "rests." Fabricius in the 16th century distinguished cancer from inflammatory swellings, urging rigid complete removal of the cancer. Severinus excised the axillary nodes along with the tumorous breast. Ambrose Paré did total excisions of the tumor and the German, Hildanus, carried out extensive dissections including the axillary nodes.

The Renaissance period (1500 to 1700 A.D.) sparked the first real impetus to the beginnings of our modern day concept of metastasis. It was during this period that Harvey discovered the circulation of blood and Olens the lymphatic system; Leeuwenhoek produced the microscope and the old religious antipathies to postmortem examinations were dissolving. Our first real coup d'état was scored early in the 18th century by LeDran when he described cancer as being a local disease in its early stages that spread via the lymphatics to the regional nodes and thence to the general circulation. So by the end of the 18th century cancer was universally accepted as a disease that did, indeed, eventually spread with implant of secondary growths, necessitating wide excision to include all involved lymph nodes and tissue.[11]

The term "metastasis" (defined as the transfer of disease from one organ or part to another not directly connected with it) was coined by Recamier in 1829 when he discovered a secondary growth of mammary cancer in the brain. It was he, too, who described local infiltration of tissues and venous invasion. Virchow, to whom we are indebted for the basis of cellular pathology which spelled the death of Galen's humoral theory, admitted the possibility of—but did not subscribe to—cancer cell transport via the blood and lymphatics. Instead he espoused the thesis that tumors contained a fluid, which he termed "parenchymatous juice," which carried tumor cells to more distant parts of the body. He

recognized that this "juice" could pass through the lungs without implant of secondary growth and yet set up malignant changes at more remote sites.[11]

It remained for Thiersch and Waldeyer in the late 19th century to dismiss Virchow's thesis of tumor cell suspension in a "parenchymatous juice," ascribing the occurrence of secondary growths or deposits of cancer to the phenomenon of dissemination, or metastasis, via blood and lymph transport of cell emboli. The mechanical theory was gaining favor at this same time, its chief proponent being von Recklinghausen who stressed retrograde flow in the lymphatics caused by obstruction and collateral channels. Stephen Paget first described the selective affinity of cancer cells for certain organs, the origin of the thesis of favored "soil" being the determinant for eventual germination of a secondary growth, a thesis expounded further by contemporary 20th century investigators Willis and Ewing.[5]

The concept of "lymphatic permeation" in which it was theorized that cancer cells escaped into serous cavities, pleura or peritoneum, were distributed by gravity of visceral movements to eventually become implanted on the serous surface of viscera was advanced by Handley in 1906.[5]

The thesis of athrepsia, originally advanced by Ehrlich, in which immunity to tumor implant was ascribed to lack of necessary nutrient material was given further credence by Clunet in 1910. Clunet hypothesized that removal of the primary increased nutrient supply needed for secondary growth deposits.[9]

Levin and Sittenfield (1911) could not subscribe to the thesis of athrepsia.[5] Up to this time varying views of different pathologists held that specific affinity of cancers for certain metastatic sites was either due to chemical constitution of the recipient organ, the morphologic structure of the organ, the fact that the walls of the bone marrow were thin and noncollapsible, or to the size of the cancer cells relative to the minute size of blood vessels of an organ. Through their experimental investigations with small animals, they found no evidence to suggest that the morphologic structure of the transport channels had any effect on the cancer cell; that location of metastatic deposits in different tumors was due to a specific affinity of cancer cells to the cells of different organs.[5] They concluded that the main factors determining localization and frequency of metastasis were the character and malignancy of the cancer cell and the general and local susceptibility of the host organism, and that the failure or success of proliferation of cancer cells transported from the primary site was the result of an interaction of these two factors.

ROUTES OF SPREAD

From this background have evolved certain undisputed and established facts about cancer. We know, for instance, that the route of spread from the primary focus usually follows a foreseeable and predictable pattern in certain types of cancers. There is, for instance, almost no malignant tumor in which local extension of the tumor or invasion to the immediately contiguous tissue structures does not occur.[4] From this invaded bed cell emboli break off, penetrate the walls of blood vessels, migrate by one of various routes and become arrested in capillaries or arterioles. The cancer cell embolus, or group of cancer emboli, or most usually a clump of cancer cells, is transported by either of three routes—the vascular system, the lymphatic channels, or by transcoelomic mechanics—to other tissues and organs remote from the primary focus, there to set up (or not, depending on multiple factors) secondary tumors or metastatic tumor deposits.[10] It is known that most carcinomas are transported via the lymphatics and less frequently by way of the blood vessels, principally the veins. The reverse is true in the transport of most sarcomas.[6,12] The traditional concepts of cancer autonomous growth with constant, progressive spread throughout the life of the host and its dependency upon the host alone for its blood supply and that early

treatment is synonymous with cure, and conversely, that late treatment is of little or no avail have long been recognized as untenable.[2]

Clinical recognition of the most frequent sites of preference for metastasis (of a thyroid cancer for spread to bone, of a breast cancer to lung, of a liver cancer to brain, or of a melanoma to small bowel mesentery) stimulated investigations directly resulting in greatly expanded knowledge in and understanding of the transport routes of spread.

This knowledge of the usual routes of spread of specific tumors frequently is of significant help in locating an unknown primary lesion, since the first symptom of disease often will be lymph node involvement.

CANCER CELL CHARACTERISTICS

The cancer cell possesses characteristics unique to it that give it capability of spread. These are its mobile, ameboid-like movement, its lack of adhesiveness making it capable of detachment from a tumor growth, its ability to multiply and proliferate, its lack of maturation, very probably an intrinsic spreading factor, similar to hyaluronidase, and probably a defect in cell surface membrane. The decreased adhesiveness of cancer cells is thought to be due to some alteration in their chemical makeup, their decreased calcium content, and their elevated potassium levels.[4] Other factors believed to affect the ability of the cancer cell to metastasize are morphologic characteristics specific to it, different from those of the normal cell; its rate and duration of growth; a latent (or dormant) stage feature present in varying degrees before the cancer becomes clinically manifest.

Factors now known about cancer are the premises on which we base our therapeutic assault on systemic spread. We know that increased host resistance decreases cancer cell spread; that host resistance can, to some degree, be increased through containment of the cancer at the site of origin; that supportive measures to shore up the host's general physiologic defenses can lessen priority demands of cancer cells; that most cancers are present in the microscopic, preclinical state; that some cancers have a specific affinity for spread to certain organs or structures; that there are basically two types of cancer—local and systemic; and that certain cancers are slow growing and others rapidly progressive.

Variability in the biologic behavior of different cancers heightens the complexity of dealing with systemic cancer. Answers to the questions posed by this variability have been sought from many angles, many of which directly triggered the development of all these new basic science disciplines and subdisciplines.

PRESENT PHILOSOPHY AND MANAGEMENT OF SYSTEMIC CANCER

Prior to the realization that all cancer is present in a preinvasive, or preclinical, phase the major thesis of therapy for cancer was first to detect and diagnose the disease at the earliest possible stage; then to attack the local tumor with the most radical approach possible.

Just a short 20 years ago evidence of wide invasive spread and metastasis was sufficient to negate any definitive therapy. The diagnosis was a cut and dried "nonresectable" and the patient was, for all intents and purposes, relegated to the realm of terminal, eligible for nothing more than palliative analgesia and sedation. Fortunately, this do-nothing attitude for systemic cancer has gradually given way to the institution of more hopeful and successful procedures. We are making inoperable primary tumors capable of resection through the use of preoperative irradiation and/or chemotherapy designed to shrink these tumors so they can be excised surgically. This makes possible both prevention of further seeding of the cancer by the primary lesion and, by eliminating its priority nutrient demands, gains time for the body host to build up its reserves for resistance to secondary growths. Thus the therapist, be he surgeon, radiotherapist, chemotherapist,

or internist, can direct his full therapeutic energies towards an intensive attack on the systemic disease.

Where are we today in the art of therapeutics for systemic cancer? We use four major avenues of approach—hormonal therapy, chemotherapy, radiotherapy and immunotherapy—alone or in combination aimed either at cure or containment. However, we are following a single file pattern of attack, aimed not toward systemic cancer therapy *per se*, but rather treatment of metastasis relative to its specific primary focus, its histologic type and biologic nature, its usual pattern of spread, its tendency or frequency to arrest and develop secondary tumors in distant sites, its known predilection for certain seats of metastatic domain. And from this base, we proceed to the specificities of therapy for that particular metastatic cancer, be it from the breast, the cervix, or whatever site of origin. We tend not to look on metastasis in the concept of a specific disease entity; namely, systemic cancer.

An understanding of the correct initial treatment, including selection of the best modality, adequately administered will frequently eliminate the local disease and markedly reduce metastasis. A typical example of what often happens is seen in patients with soft tissue sarcomas, too many of whom, on first admission to our institution, present with a history of from one to three inadequate attempts at surgical removal followed by recurrence.

DETECTION AND DIAGNOSIS

Patient delay is still the highest deterrent to early diagnosis, in spite of the fact that most cancers are detected first by the patient. But also too many physicians fail to attach sufficient importance to the less obvious but nonetheless tell-tale symptoms of cancer in their patients. Harried physicians also often neglect to carry out even some of the more simple procedures during a routine physical examination which could lead to detection of an early cancer.

Whatever the reasons for either patient delay or inadequate physician examination, implicit is the need for a renewed impact in education of both the patient and the physician in the possibilities of cancer control which are available right now. A barrage of communication to educate the patient not through the negative approach of fear, but rather with a positive appeal of hope for cure might serve to stimulate earlier self-referral. A similar appeal to the physician, pitched positively toward the possibilities for cure now available through sophisticated research therapy might serve to stimulate renewed efforts of more thorough adequate examinations, with proper referral of his patient if indicated.

TREATMENT

René Dubos once said "We can no longer afford to wait on complete scientific fact before we act. To wait is social suicide." This maxim is particularly applicable to cancer therapy. Acting on the skill and knowledge we already have, being willing to abandon those modalities which have proven ineffective, having the courage to try ingenious combination modalities, we are now able to offer our patient effective therapies—some of them curative—that were not even thought of 10 years ago.

Surgery. The limitations of radical surgical attack and the stages of disease where radical surgical attack is worthwhile have been defined. Adjunctive chemotherapy and radiotherapy have shrunk inoperable tumors, making possible their surgical excision. We have been able to abandon surgical therapy entirely for some cancers, having achieved superior results with less drastic modalities of chemotherapy and/or radiotherapy. With increasing knowledge and earlier, better diagnosis, we can reduce the extent of some established radical surgical procedures, and expand our innovations in surgery used in combination with other therapeutic modalities. Supportive measures to enhance surgical therapy, such as careful patient selection, second-look operations, technical refinements (*i.e.*, ileal conduit urinary diversion, transperitoneal lymphadenectomy, etc.), antibiotics to control infection, physiologic postoperative

care with maintenance of electrolyte balance, blood replacement, and control of wound infection, superb anesthesia and endocrine gland ablation now permit the most effective use of radical surgery when indicated. We can expect further improvement only through making these techniques more universally available.

Chemotherapy. Generally speaking we have achieved no cure of cancer through chemotherapy with two possible exceptions, the chorioepitheliomas and Burkitt's tumor. In spite of discouraging effects of chemotherapy as a curative, anticancer agents have nonetheless produced enough other promising results to justify our continuing search for new and better agents. The use of chemotherapy alone in the treatment of patients with advanced (inoperable or recurrent) carcinoma of the ovary where the lesion is 3 cm. or more in diameter has been very encouraging.[1] Chemotherapy has produced numerous instances of complete remissions with no detectable evidence of disease by current evaluation methods. The rising percentages of cures, remissions, and tumor regressions attained by chemotherapy in the past 10 years, particularly in acute lymphocytic leukemia in children, graphically illustrate the progress and possibilities in the treatment of systemic cancer (Table 1). Generally speaking, however, the disease re-establishes predominance, progressing to its presently inevitable termination.

The aim of the chemotherapist is to destroy every cancer cell by using variations in regimens of drugs and combinations of drugs. Even if present chemicals destroy every cancer cell there is no evidence as yet to support the thesis that we have altered the basic process that allows the cell of origin to generate a cancerous offspring in the beginning or that it cannot do so again.

Radiotherapy. Quite obviously, as radiotherapists, your definitive knowledge of the progress in this therapeutic art far surpasses that of mine, as a surgeon. Therefore, I feel that any statement I make might well be superfluous under these circumstances. I would only emphasize my own personal high regard and respect for what has been done, and is being done, in radiotherapy, whether in a curative, additive or adjunctive role, for the ultimate benefit of the cancer patient. More and better full-time therapists are needed to use our present radiotherapeutic armamentarium.

The bringing into your team of radiobiologists, biophysicists, bioengineers, dosimetry experts, etc. and the engineering developments in equipment has resulted in spectacular progress in a comparatively short period of time. We do not yet have a chemotherapeutic agent that can match the ionizing beam of radiotherapy in lethality to the cancer cell, at the same time allowing the adjacent normal cell to survive.

General Principles of Treatment. Thus, the principles of treating systemic cancer as understood today include:

1. Absolute elimination of the cancer at the site of origin to decrease the body burden of cancer cells and eliminate further seeding from the primary growth. This is particularly applicable in those lesions known to threaten vital body function through obstruction (as in cancer of the colon), perforation, encroachment of the adjacent structures, and hemorrhage.

2. Use of combination therapy, such as radiation therapy and/or chemotherapy, to reduce local invasion of the cancer, thereby lessening the chances of dissemination of viable cancer cells during the more extensive surgical procedure(s).

3. Manipulation of the patient's physiology to effect hormonal stabilization or growth regression of any remaining metastatic lesions. This has been very effective for a considerable per cent of cancers of the breast, prostate, and thyroid, and to a lesser extent for cancers of the adrenal gland, ovary and testicle.

4. Definitive treatment of isolated areas of metastasis by radiation therapy, surgical therapy, and perfusion of chemotherapeutic agents.

5. Treatment of diffuse metastasis by chemotherapy.

6. Maintenance of the patient in the

TABLE I

CLINICAL CANCER CHEMOTHERAPY*

Advances in Past 10 Years

Disease	Treatment	Response
Choriocarcinoma (women)	Methotrexate, or Actinomycin D	80% cure
Testicular tumors	Actinomycin D in combination, or Mithramycin	10% cure
Burkitt's lymphoma	Cyclophosphamide, or Methotrexate	10–20% probable cure
Wilms' tumor	Actinomycin D adjuvant to surgery and irradiation	40% to 80% increase in cure rate
	Vincristine	60% remission rate
Acute leukemia (children)	Cyclophosphamide	30% complete remission
	Vincristine	50% complete remission
	Vincristine and Prednisone	85% complete remission
	Daunomycin	20+% complete remission
	Cytosine arabinoside	20+% complete remission
	Multiple chemotherapy (VAMP)	Prolonged duration of "unmaintained" remission. Six-fold increase in survival
Acute leukemia (adults)	VAMP	30+% complete remission
	Daunomycin	30% complete remission
	Cystosine arabinoside	20% remission rate
Solid tumors of childhood	Cyclophosphamide, Vincristine, Daunomycin	10% to 60% tumor regression
Lymphoma	Vinblastine, Vincristine, Procarbazine, Streptonigrin	20% to 60% tumor regression
Myeloma	Melphalan, Cyclophosphamide	20% to 60% response rate. Improved survival
Breast cancer	Fluorouracil, Cyclophosphamide	30% regression
Colon cancer	Fluorouracil	20% regression
Ovarian carcinoma	Alkylating agents	40% regression
Other "solid tumors"	Fluorouracil	10% to 20% regression
Glioblastoma	Mithramycin	10% to 30% regression
Head and neck tumors	Methotrexate infusion	30% regression

* Prepared by Dr. Emil Frei, The University of Texas M. D. Anderson Hospital and Tumor Institute at Houston, May, 1967.

best possible state of mental and physical health, hopefully aiming toward a useful productive life.

7. Maintenance of inclusive records of therapy and from their analyses the devising and implementation of comparative clinical trials.

8. Evaluation of every patient in terms of his environmental exposure to hazards of a carcinogenic nature.

9. Lifelong follow-up.

All of these approaches are designed to hold the systemic disease in abeyance, thereby gaining us time to pursue the multiplicity of leads: toward detection and diagnosis at earlier, preferably preclinical, stages of the disease; toward more effective curative therapy, both of the primary site and secondary loci; toward increasing the patient's general health and well-being; and, hopefully, to the final attainment of the ultimate aim—discovering the prime causative factor of cancer.

FUTURE OBJECTIVES

We have already materially exhausted our present resources in the area of definitive treatment. The avenues of direction in our future efforts to control cancer can be defined clearly by a look at the 5 year survival results of our present treatment methods compared to the incidence of the disease in the different sites.

Of significant interest is that 75.5 per cent of total cancer patients have cancers in sites which offer the best possibility of cure (Table II-A), while those patients who, although benefited by treatment, inevitably die of their disease, comprise only 24.5 per cent of total cancer incidence (Table II-B). This latter group includes those patients with 5 year survival rates of 5 ± per cent whose cancer is usually systemic by the time it is diagnosed. Cancers with poorest treatment results include those of the stomach, esophagus, pancreas, liver, lungs and bronchus, prostate, all leukemias, lymphoma (Hodgkin's), and multiple myeloma. Better treatment results will be realized only when more effective systemic therapy is discovered, although earlier detection by newer diagnostic techniques would undoubtedly lead to some improvement in survival rates.

In those patients best benefited by current modalities of treatment, 5 year survivals vary from 88 per cent for skin to 15

TABLE II-A

BEST RESULTS

	Per Cent of	
	Total Cancer	5 Year Survival
Skin	10.0	88.3
Lip	8.0	88.1
Corpus Uteri	5.2	57.0
Soft Tissue	2.3	50.5
Oropharynx	1.6	47.0
Cervix	11.5	45.7
Thyroid	1.2	45.4
Breast	14.1	43.2
Salivary Glands	0.9	42.3
Melanoma	2.0	40.5
Bladder	3.8	31.0
Testis	0.8	27.6
Ovary	3.5	26.4
Rectum	2.9	25.0
Colon	6.6	22.3
Larynx	1.1	15.0
Total Incidence	75.5%	

TABLE II-B

POOREST RESULTS

	Per Cent of	
	Total Cancer	5 Year Survival
Liver	1.7	2.8
Pancreas	1.7	3.8
Esophagus	0.7	3.9
Lung-Bronchus	5.3	4.4
Leukemia (All)	3.1	5.9
Stomach	3.9	7.1
Paranasal Sinuses	0.2	11.6
Lymphoma	3.2	11.7
Multiple Myeloma	0.3	12.4
Prostate	4.4	18.9
Total Incidence	24.5%	

per cent for larynx with a general over-all average approximating 40 per cent. No doubt even the survival rates in these cancers could be greatly improved if initially treated by physicians with oncologic expertise.

In those cancers where we are realizing the highest per cent of 5 year survivals, apparently our present therapeutic methods are effective. If present modes of therapy are, indeed, the main reason for these higher 5 year survival rates, they should be continued and improved by clinical research. In cancer of these sites our efforts should be concentrated toward the development of new methods of detection in the incipient stages and to find the causative factors, in order to increase the effectiveness of our curative therapy.

Our greatest opportunity for immediate improvement of cancer care lies in this "best results" group. But this improvement depends upon the creation of cadres of oncologically oriented physicians working in an environment where their major efforts can be devoted to the cancer patient and where new fundamental knowledge in the field is continuously converted to practical bedside application. We must promote and foster recognition of the need for specialty training to treat cancer properly.

Patients in the "best results" group who are not surviving 5 years are those whose cancer has become generalized. While we are seeking ways to cure systemic cancer we should find some way to keep the cancer localized in these patients, not to let it become systemic, through better diagnosis, furthering the present modalities of treatment through using combined therapy in addition to surgery, radiotherapy, chemotherapy and in combining all these with the team approach.

In those cancers where we are realizing the lowest percentages of 5 year survivals, our present methods of therapy are quite obviously ineffective, and here our efforts must be concentrated on the development of new treatment methods. It is also obvious that, in these cancers, the disease has already been disseminated suggesting that it was present for a long period of time in a preclinical stage. Therefore, efforts to develop new methods for improving detection at the preclinical level should be carried out. Removal of the primary tumor in these cancers should be done, wherever possible, to concentrate on an intensive attack on the disseminated disease.

DETECTION AND DIAGNOSIS

In the area of detection and diagnosis alone, where the goal is for earlier detection, preferably preclinical in point of time, and more immediate, definitive diagnosis, research in new techniques of diagnostic radiology, diagnostic cytology, laboratory analyses, epidemiologic and demographic trend studies, and the institution of more adequate and thorough physical examinations must be intensified.

Further refinements in lymphangiography, for example, can provide knowledge in more than one dimension. Primarily used in diagnosis, this procedure nonetheless can serve to further detail the routes of spread of cancer emboli; it can outline the extent of metastatic lymph node involvement; it can monitor the effectiveness of treatment whether by chemotherapy or irradiation; it can finely delineate the perimeter of both the primary and secondary disease thereby serving as an invaluable aid to precise radiotherapy; it can, perhaps, help to resolve the role(s) of lymph node function. That other uses, functional to our understanding of cancer, will come from lymphangiography is certainly a possibility.

Future studies in exfoliative cell cytology may result in diagnostic methods for the detection of cancer of other sites equally effective to those we have already for cervix, lung, and stomach.

Ecology, which is concerned with the understanding of the mechanism of carcinogenesis, whether from exogenous or endogenous factors, whether a chemical or vegetable agent, or an infectious or genetic process or, as is more likely, a combination of two or more of them, offers a broad base for solution to the problem of cancer. These

avenues of carcinogenesis now appear to be converging together with radiation exposure, viral oncogenesis and chemical carcinogens in showing similar effects on the chromosome. The propagation of cancer in man by his environment becomes an increasing challenge for its control and even its prevention.

Possibly the most exciting prospect in cancer is the development of diagnostic techniques capable of detecting the disease before it becomes clinically apparent.

TREATMENT

One example of present-day therapy that might be applicable for the immediate future is our method of treating thyroid carcinoma of the papillary-follicular variety. Since radioactive iodine was shown to be absorbed by and capable of destroying normally functioning thyroid tissue we have attempted to cause thyroid cancer to mature to the point of physiologic function where it would absorb radioactive iodine. We use this procedure in patients with metastatic lesions by total removal of the thyroid gland, allowing the patient to become myxedematous. The physiologic demands of the body for thyroxin cause the metastatic lesions to function to the extent of absorbing a therapeutic dose of I^{131}, thereby controlling any further viability of the cancer cells in a very appreciable number of patients. The principles involved here will be studied for their possible application to other sites and kinds of cancer. It is possible that metabolic variations in other tissues can be exploited for similar control of growth, maturation, and differentiation of individual cancer cells. Such manipulations could permit either peaceful coexistence of the cancer with the host or enhance host resistance to reproductive turnover and dissemination of the cancer cell to distant sites.

The future in surgical therapy lies in overcoming the immunologic barrier to organ transplantation. Much has and can be learned from the rather extensive experience thus far in renal transplants in which 75 per cent success has been realized in monozygotic twin donor organ transplants. The problems of donor source, organ storage, physiology, surgical techniques, generalized metastasis and ethics in transplantation procedures can be eventually resolved. The actual surgical techniques of organ transplants need to be perfected. Stored organ banks are a definite possibility. Promising progress has already been made in the area of minimizing the ischemic period, thereby maintaining donor organ viability for longer periods of time.

Present progress in the treatment of soft tissue sarcomas with radiotherapy given under tourniquet-induced anoxia, heralds encouraging advances in future therapy. In a series of 13 patients from our institution who have received this type of radiotherapy regimen in total dosages of 14,000 rads, there have been no recurrences and only a minor complication in 1 patient. Nine of these 13 patients are now 1 year or more post treatment, with the longest survival 34 months in 1 patient.

Another recent investigative study using mice to test the effectiveness on enhancement of radiotherapy with the use of hyperbaric oxygenation has produced similar encouraging results. Four types of implant tumors were used in this experimental investigation—2 types of mammary carcinoma, 1 fibrosarcoma, and 1 squamous cell carcinoma. It was found that administration of a therapeutic dose of irradiation given in air sufficient to produce cures in 10 per cent of these implant tumors resulted in cure frequencies ranging from 43 to 95 per cent of the tumors when given under conditions of hyperbaric oxygenation at 3 atmospheres absolute.[8]

Although hormonal therapy is used today, both in additive and ablative roles, in treatment of systemic cancer, there is still more to learn about the specifics of hormonal function in relation to its effectiveness in cancer therapy on either enhancement or inhibition of tumor growth.

The time factor relative to the use of manipulative hormonal procedures in the total treatment sequence needs to be clearly delineated, in order to find out

when, and when not, to employ hormonal procedures in coordination with other therapeutic modalities to produce the greatest degree of long-term survival in our patient. Further clarification is needed to determine just which tumors are endocrine dependent, and whether ablative measures will enhance the over-all therapy, or conversely, cause more rapid progression of the disease.

That immunologic factors play a significant role in cancer was first recognized in 1905 when Clowes described the spontaneous regression of a grafted tumor and showed that such animals are refractory to reinoculation. Woglom in 1913 expressed the phenomena of immunity as genetic differences between host and recipient.[3] Although spontaneous regression of human tumors is rare it is probably due to the development of auto-antibodies. It is conceivable that some tumor cells possess an auto-immune mechanism that would depress or retard their proliferation and metastasis.

Our significant progress in immunization for numerous communicable diseases portends possibilities of similar discoveries in the immune mechanism of cancer. The possibility of a cancer vaccine should stimulate our research in immunology toward intensive searches for tumor-specific antigens.

One of the greatest obstacles we face in our progress against the cancer problem is the considerable period of elapsed time with laboratory findings remaining in a latent or dormant stage before their adaptability to possible clinical use. An outstanding example was that in the recent widely publicized account of the treatment of a leukemic child with L-asparaginase at the Wadley Research Institute in Dallas. Fourteen years ago, in 1953, J. G. Kidd first showed that animal lymphomas would regress, both during *in vitro* culture and *in vivo* treatment with normal guinea pig serum. This inhibitory activity of guinea pig serum was subsequently confirmed by several other investigators including Broome who, in 1961, demonstrated that the asparaginase reaction of guinea pig serum was correlated with its antitumor activity. L-asparaginase derived from *Escherichia coli*, a much less expensive source than guinea pig serum, was reported in late 1966 and ongoing studies to purify the *E. coli* in order to reduce antigenicity are promising.

In summation, our best approach today to an attack on systemic cancer, once established, is a concerted, cooperative team effort concentrated on (1) the establishment of a definitive diagnosis, to include determination of the extent and locale of metastatic deposits, (2) specific initial therapy adequate to assure absolute eradication of the disease at the local and regional sites, followed by (3) specific therapy aimed at the systemic disease with eradication of all secondary metastatic deposits, if possible, or if not, containment at a subclinical level.

DIRECTIONS TOWARD ATTAINMENT OF FUTURE OBJECTIVES

The prime direction of our future objectives in the control of cancer should lie in learning how to overcome the natural barriers to host resistance, learning how to increase the degree of host resistance by attenuating the cancer at the site of origin, and in discovering mechanisms to inhibit the proliferation and division of the cancer cells through a better understanding of the host's natural physiologic defenses.

A continued pursuit of more and better agents to destroy cancer cells or to cause them to maturate should be carried on. Continued investigation into the immunologic and hormonal factors leading to increased host resistance should be intensified. There should be increased efforts toward better information and understanding of the biologic behavior of specific cancers, finding out which ones tend to remain localized, which tend to spread. There must be further pinpointing of specific organ affinity to become seats of secondary deposits, and from what primary locus these most frequently originate, with determination of which of these has the better chance to prolong life. More extensive studies

should be carried out on the time factor of latency or dormancy, particularly in asymptomatic populations but also in those patients with arrested disease with known tendencies to recur months or years later. Determinations should be sought of what effect, if any, the transport fluids of blood and lymph and their channel or vessel structure has on the in-transit cancer cell.

We are missing a tremendous and little appreciated opportunity to make our scarce manpower effective in an unknown but decidedly greater dimension of productivity. We must use to the fullest capacity available technology for automation, new materials, recently learned physical forces and sciences, mechanical and chemical phenomena which have yet to be applied to biomedical research and medical techniques for better care of the sick and prevention of disease. We could now, with proper funds, design and build the teaching-research center of tomorrow, incorporated into a super hospital facility as radically different as the spaceship of tomorrow. A design to coordinate this possibility can only be done in the United States and would include the use of:

1. Automation and computerization of information, daily activities and records to provide a current audit of progress and for constant patient surveillance.
2. Mechanization of transport and service activities.
3. The use of reverse isolation techniques, such as life island or laminar flow control of environment, including bacteria, making possible studies in human immunology and host resistance which are now only theorized, but so obvious that replacement of human organs and vital parts could be done before the end of this century.
4. Bioengineering and environmental health research science for continuous consideration of all possible avenues leading toward human betterment in a material world.
5. On-line coordination of basic research with clinical medicine applied directly to patient care.

In spite of our need to expand and extend cancer control through intensive efforts in the direction of these future objectives, our progress in cancer diagnosis and treatment has been phenomenal when one takes a long-range backward look. Just since the turn of the century, which was shortly after the discovery of radium, we have accomplished these things in cancer:

1. We have defined the usefulness and role of radical surgery.
2. We have developed megavoltage radiation therapy and radioactive Co^{60} in teletherapy units, probably the greatest single advance since the discovery of radium, which brings megavoltage availability to the community level.
3. We have begun to use planned combined therapy.
4. The advent of chemotherapy has made the internist a part of the cancer team and has introduced the treatment of systemic cancer. The patient with systemic cancer is being treated with hormones, cortisone, chemotherapy, and general supportive therapy. We have now brought in an attack on systemic cancer while the two major therapies—surgery and radiotherapy—have been attacks on the local nidus which must be continued for improvement of the ill patient today.
5. The development of early detection of cancer of the cervix and, hopefully, other areas by the developments in cytology (Papanicolaou).
6. New, truly fundamental medical and life science disciplines have been developed, such as molecular biology and medical genetics, in their broadest dimensions, and combined with clinical research and developmental therapeutics will find the way for the conquest of systemic cancer.

CONCERTED ATTACK ON THE TOTAL CANCER PROBLEM

This progress has been achieved primarily through the mechanism of coordinated cancer activities of the categorical cancer institute and (to a lesser extent) in the medical school research hospital setting. Only in this kind of setting, where the basic scientist works along-side the clinical phy-

sician can there be organized efforts to bring research results directly to the bedside, with the least delay possible, negating the time lag between basic and applied science.

We need many more such facilities for cancer services where a concentration of patients can be obtained, available for better teaching, demonstration, research and service. Major metropolitan areas must develop such centers, actively affiliated with university teaching programs, but with rigid maintenance of their internal administrative and budgetary independence for maximum effectiveness.

There is need for more innovation, more ingenuity, and much inventiveness through investigative research in our concerted attack on the total cancer problem. No scientific discipline, be it fundamental or clinical, is immune from the continuing need for improvement through development of better and faster means to analyze qualitatively both its current and future methodologies, tenets, and results. Future attacks on the cancer problem must embrace the intensive pursuit of the limitless leads we already have plus any more, not yet thought of, that hold promise, no matter how minute, for a key to the cancer puzzle.

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SOME OBSERVATIONS ON THE COMBINED EFFECTS OF X-RAYS AND METHOTREXATE ON HUMAN TUMOR CELLS *IN VITRO* WITH POSSIBLE RELEVANCE TO THEIR MOST USEFUL COMBINATION IN RADIOTHERAPY*

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THERE are only a few situations in which the combination of chemotherapy with radiotherapy can be justified in the treatment of localized malignant disease, particularly if the concurrent use of a chemotherapeutic agent enforces a scheme of dose-fractionation unfamiliar to the radiotherapist. Friedman[10] has pointed out that "in combining chemotherapy with radiation, we want to save lives, not rads." To achieve this, the chemotherapy must increase the *therapeutic ratio* between effects on tumor and those on normal tissues in the radiation field. It can do so in one of several ways, *e.g.:*

(1) By shrinking the tumor mass rapidly so that a course of fractionated radiotherapy finds more tumor cells in well-vascularized areas and hence more sensitive to radiation effects than hypoxic cells in near-necrotic regions of large tumors.

(2) By potentiating the effect of radiation upon the anoxic or hypoxic cells in tumor more than the effect upon the well-oxygenated cells of normal tissues.

(3) By protective effects upon normal tissues, assuming that the more poorly vascularized areas of tumor will not be protected equally, etc.

Clinical evidence has been presented that methotrexate can act in the first of these ways,[11] and in earlier radiobiologic studies, we have shown that it can act in the second.[1] Although a considerable volume of clinical experience with this drug used both sequentially with radiotherapy[11,12] and in simultaneous combination[6,7,11,12] has already been reported, the present laboratory studies lead to new suggestions for the optimal use of methotrexate with radiotherapy.

EXPERIMENTAL METHODS

I. CELLS

HeLa S-$3_{oxf.}$, descendants of a clone isolated in 1963 and originally obtained from a human cervical carcinoma, have been used in these studies. They have been grown in medium 199 (Glaxo) supplemented with 15 per cent human type AB serum. In this medium, they attach readily to the polystyrene surface of 'Falcon TC' or 'Nunclon' disposable Petri dishes and grow from single cells into clones with a population doubling time now averaging 30 hours. There is a wide spread of rates of growth of individual clones[3] so that although trypsinization and plating produces a degree of synchrony in the passage of cells through their first post-plating division,[4] this synchrony is rapidly lost in unirradiated clones.[2] Petri dishes on which cells were grown were incubated at 37°C. in a humidified CO_2 flow incubator which maintained a constant 5 per cent CO_2-95 per cent air environment. They were fixed and stained when the average clone size was 2 mm. (an incubation period of 14–18 days, depending upon radiation dose) so that slowly-growing 'small clones' would not be overlooked. The stained dishes were examined under

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21× stereomicroscopy and all clones containing more than 32 nongiant cells were scored as reproductively intact.

II. IRRADIATION

The cells were irradiated in perspex or brass containers, using 250 kvp. x-rays from two generators situated equidistant above and below the Petri dishes. The focus-object distance was 50 cm., the half value layer 1.3 mm. Cu, and the dose-rate 130 rads/min. in the perspex containers and 43 rads/min. in the brass (gas-tight) containers, as measured by ferrous sulphate dosimetry.

III. GASEOUS ENVIRONMENT FOR IRRADIATION

For irradiation under *oxygenated* conditions in either the perspex or brass containers, humidified 5 per cent CO_2-95 per cent air was circulated over the Petri dishes prior to irradiation, and the container was then sealed during the actual period of irradiation. For *anoxic* irradiation, only the gas-tight brass containers were used; they were fitted with high-vacuum taps and their brass lids were sealed by the uniform compression of neoprene 'O' rings, using 6 wing-nuts spaced evenly around the circumference of each lid. Humidified 5 per cent CO_2-95 per cent nitrogen ('White Spot' purity, supplied by the British Oxygen Company, Ltd. and containing less than 10 p.p.m. residual oxygen contamination) was circulated through the containers at a flow rate of 150 ml./min. for 6 hours, and the effluent gas was monitored for residual oxygen concentration by means of a Hersch cell.[13,14] During this gassing period, the brass containers were totally immersed in a water bath maintained at 37°C. Under water, the vacuum taps on the brass containers were sealed immediately prior to irradiation. The nylon connecting tubing was removed and the containers were allowed to cool to room temperature and then irradiated in the same manner as for oxygenated conditions. The oxygen concentration in the effluent gas immediately prior to sealing the brass containers was less than 15 p.p.m., and the prolonged gassing period was sufficient to ensure adequate de-oxygenation of the liquid medium.[16] Following irradiation in either gaseous environment, the cells were immediately returned to the humidified CO_2-flow incubator and maintained at 37°C. for clonal growth.

IV. ADDITION AND REMOVAL OF METHOTREXATE

Methotrexate (4-amino-10-methylpteroyl-glutamic acid, Lederle) was freshly dissolved in sterile distilled water prior to use. It was diluted appropriately in sterile normal saline and added to the complete plating medium at the time of plating the cells, or at subsequent times by removing the medium (using a Pasteur pipette and producing minimal agitation), and gently washing the Petri dishes with warmed medium 199 without added serum. This wash solution was then gently aspirated by Pasteur pipette and the warm complete plating medium containing the methotrexate was added. For removal of methotrexate from the plating medium, a similar procedure was followed; aspiration of the MTX-containing medium, followed by one wash in warmed medium 199 without serum, followed by addition of warmed complete plating medium. In all the experiments described in this communication, the MTX was allowed to remain in the medium for only 24 hours.

RESULTS

I. CELL-KILLING BY METHOTREXATE ALONE

(a) *Effect of dose of drug.* A 24 hour incubation in medium containing concentrations of MTX below 0.03 μg/ml. did not reduce the plating efficiency of HeLa cells below that of untreated controls in the same experiment. Above this concentration, however, loss of cell reproductive capacity was approximately related to the concentration of the drug in the medium until a minimum survival value was reached at a concentration around 0.3

μg/ml. MTX concentrations larger than this, maintained in the medium for only 24 hours, did not result in an increased proportion of cell death in these human carcinoma-derived cells; this is shown in Figure 1.

(b) *Effect of time of exposure to drug.* The percentage of cells which was killed by the high concentration of MTX in the growth medium of 0.3 μg/ml. was dependent upon the time for which the cells were allowed to remain in contact with the drug: this is shown in Figure 2. Two experiments are compared, one in which the MTX was added at the time of plating (*lag* phase of growth), the other in which the drug was added 18 hours later, when the cells were beginning active growth (*log.* phase). For actively growing cells, some cell-killing was seen even after the shortest periods of incubation with the drug; the delay before cell-killing occurred in lag phase cells corresponded to the time in which the cells failed to synthesize DNA during their post-trypsinization period of re-attachment.[4]

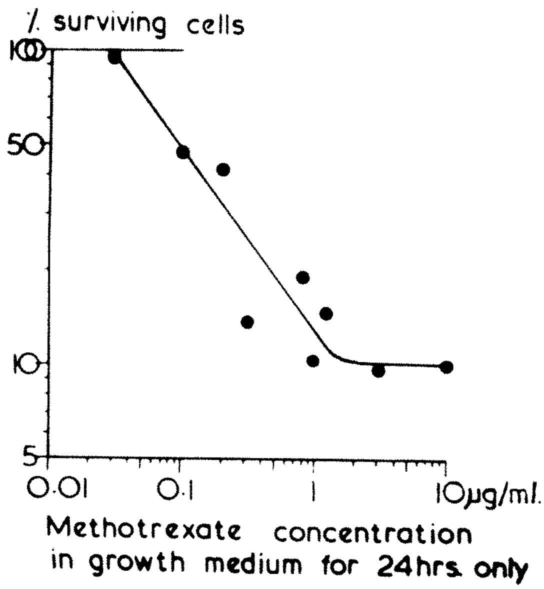

FIG. 1. Survival of reproductive capacity (ability to form clones) of HeLa S-3_{oxf}. cells exposed to methotrexate, added to the medium at the time of plating and removed 24 hours later.

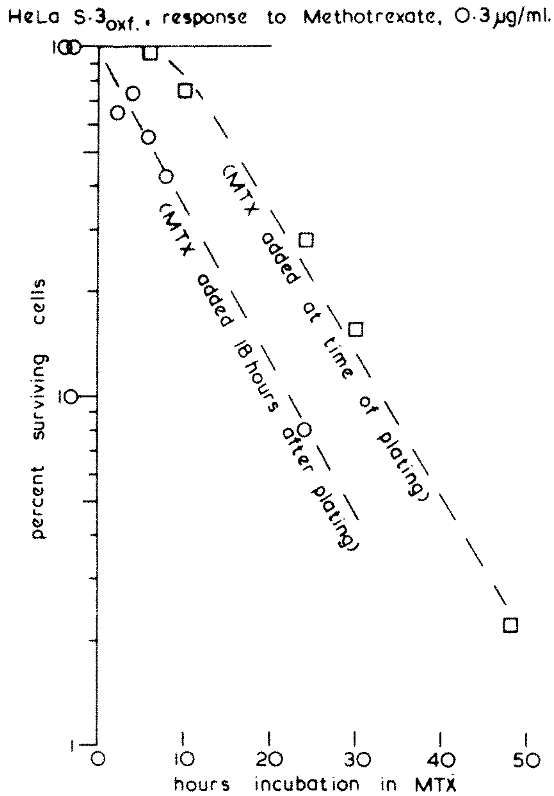

FIG. 2. Survival of reproductive capacity of HeLa S-3_{oxf}. cells after incubation in medium containing methotrexate, 0.3 μg/ml. for various periods.

II. POTENTIATION OF RADIATION RESPONSE BY CONCENTRATIONS OF METHOTREXATE WHICH DO NOT PRODUCE ANY CELL-KILLING ON THEIR OWN

After 24 hours' incubation in medium containing MTX at a concentration of 0.01 or 0.03 μg/ml., concentrations which did not produce any appreciable cell-killing on their own, the x-ray dose-response curve for cell reproductive survival was markedly steeper than that for cells irradiated at the time after plating which had not been exposed to the drug; this is shown in Figure 3. The potentiation of x-ray effects by these low doses of MTX occurred equally when the irradiation was given under anoxic conditions, so that there was no change in the *Oxygen Enhancement Ratio* (OER) when compared with the OER for cells irradiated at the same time after plating which had not been exposed to the drug; this is shown in Figure 4, *A* and *B*.

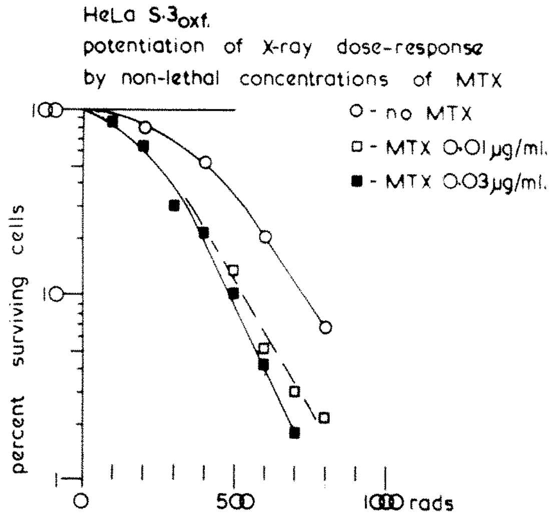

Fig. 3. Potentiation of x-ray dose-response for survival of reproductive capacity of HeLa $S\text{-}3_{oxf.}$ cells irradiated 24 hours after plating in growth medium containing concentrations of methotrexate which by themselves produced no cell-killing. The drug was removed from the medium immediately after irradiation.

III. MODIFICATION OF RADIATION RESPONSE AND OXYGEN ENHANCEMENT RATIO BY HIGH CONCENTRATIONS OF METHOTREXATE

Those cells which survived 24 hours' incubation in medium containing 0.3 μg/ml. of MTX showed a steeper x-ray dose-response curve than did cells not exposed to the drug but irradiated at the same time after plating. In addition, the x-ray survival curve for the MTX-treated cells showed a much-reduced 'shoulder'; this is shown in Figure 5, *A* and *B*. There was an even more marked steepening of the x-ray dose-response curve for MTX-treated cells irradiated under anoxic conditions. This resulted in a reduced OER, as is also shown in Figure 5, *A* and *B*. The changes produced by MTX in the x-ray response of HeLa cells which survived 24 hours' incubation in the presence of the drug proved impermanent. Cells exposed to 0.3 μg/ml. of MTX in the medium for 24 hours were given a further 2–24 hours incubation in complete plating medium without the drug and then irradiated. The pattern of change in radiosensitivity which was obtained varied somewhat between experiments, and was influenced by whether or not excess thymidine (10 μg/ml.) was added to the plating medium after the removal of the MTX. As early as 2 hours after the removal of methotrexate from the medium, HeLa cells showed increased radioresistance, and in all experiments their radiosensitivity

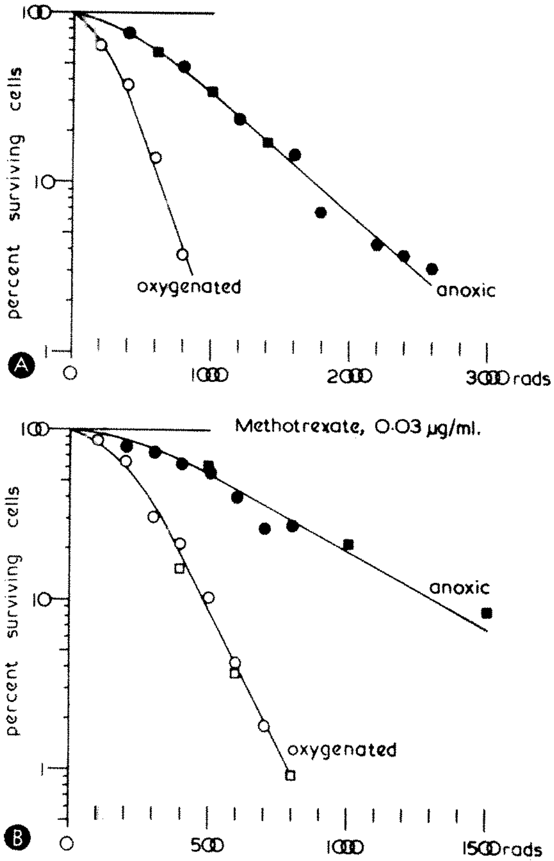

Fig. 4. (*A*) X-ray dose-response for survival of reproductive capacity of HeLa $S\text{-}3_{oxf.}$ cells irradiated under oxygenated or anoxic conditions 24 hours after plating. Each different-shaped symbol represents a different experiment, closed and open symbols of the same shape represent data obtained in the same experiment. The curves are drawn by eye. The *oxygen enhancement ratio* (OER) at the 10 per cent survival level is 2.6. (*B*) X-ray dose-response for survival of HeLa $S\text{-}3_{oxf.}$ cells irradiated under oxygenated or anoxic conditions 24 hours after plating in medium containing methotrexate, 0.03 μg/ml. The oxygen enhancement ratio at the 10 per cent survival level is 2.8. The drug was removed from the medium immediately after irradiation.

was similar to that of cells which had not been exposed to the drug by 16 hours after removal from the medium. Thus, when irradiation was delivered under oxygenated and anoxic conditions, 24 hours after the removal of MTX from the medium (48 hours after plating), the slopes of the survival curves were identical to those for cells unexposed to the drug and irradiated at the same time after plating, and the OER had returned to its normal value of over 2.5. This is shown in Figure 6.

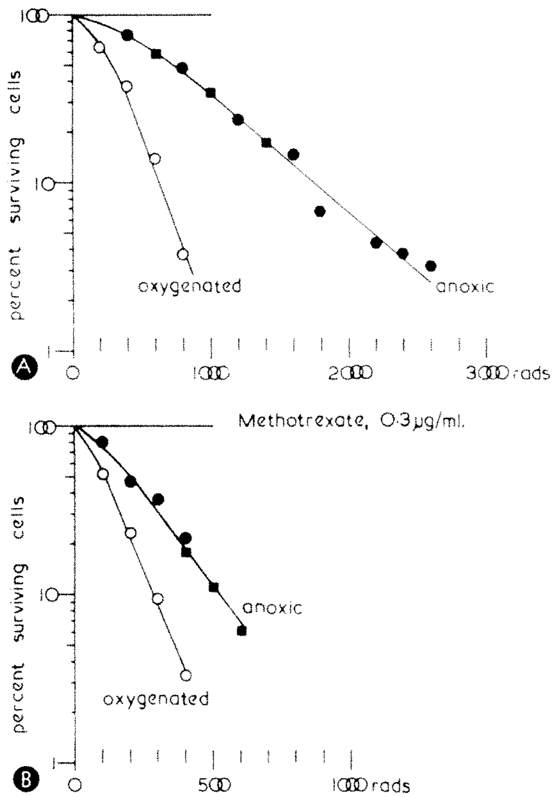

Fig. 5. (*A*) X-ray dose-response for survival of reproductive capacity of HeLa S-$3_{oxf.}$ cells irradiated under oxygenated or anoxic conditions 24 hours after plating. These data are the same as are shown in Figure 4*A*. The oxygen enhancement ratio at the 10 per cent survival level is 2.6. (*B*) X-ray dose-response for HeLa S-$3_{oxf.}$ cells surviving 24 hours' incubation in medium containing methotrexate, 0.3 μg/ml., added at the time of plating. The oxygen enhancement ratio at the 10 per cent survival level is 1.8; this represents a 'gain factor' for the killing of anoxic cells of over 1.4. The drug was removed from the medium immediately after irradiation.

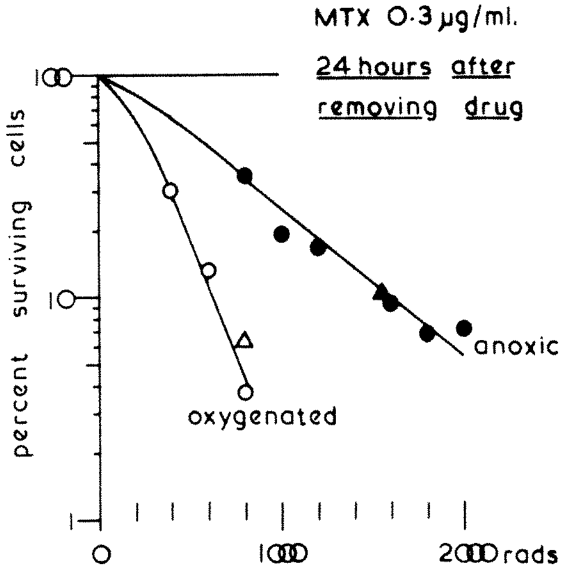

Fig. 6. The circles represent the dose-response for HeLa S-$3_{oxf.}$ cells irradiated under oxygenated or anoxic conditions 48 hours after plating, 24 hours after the removal of methotrexate, 0.3 μg/ml., which had been added to the medium at the time of plating. The oxygen enhancement ratio at the 10 per cent survival level is 2.5. The triangles represent two x-ray survival points obtained in the same experiment for HeLa S-$3_{oxf.}$ cells irradiated 48 hours after plating, but unexposed to methotrexate.

IV. EFFECT OF METHOTREXATE ON RECOVERY BETWEEN FRACTIONATED X-RAY DOSES

(a) *Non-killing drug concentrations.* Even after 18 hours' incubation in medium containing MTX at a concentration of 0.03 μg/ml., HeLa cells exposed to a 2-fraction course of 300+300 rads separated by 0–6 hours showed early recovery from sublethal x-ray damage. This is shown in Figure 7, where *recovery factor* is the increase in the fraction of surviving cells compared with the fraction surviving a single dose of 600 rads delivered at the same time after plating.

(b) *High concentrations of MTX which produce cell-killing.* If the first x-ray dose was delivered immediately after the addition of MTX to the growth medium, some recovery was seen between x-ray doses delivered 2–8 hours apart. There was an increase in the fraction of cells surviving

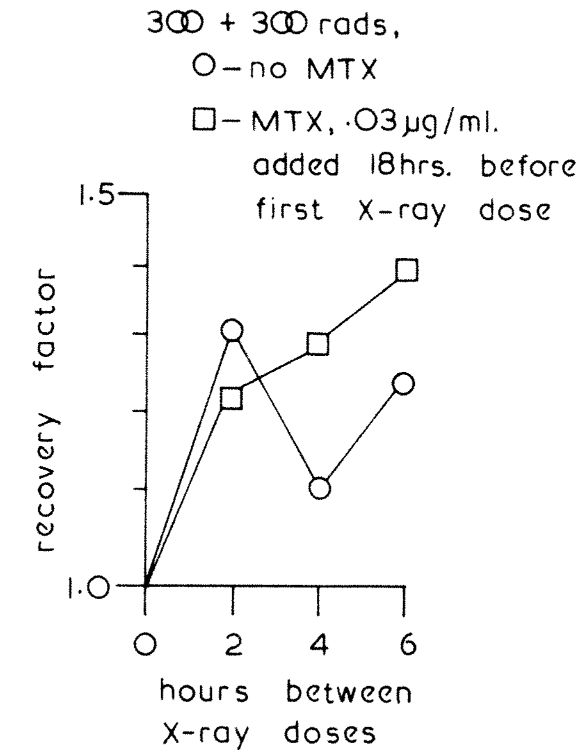

Fig. 7. Early recovery from sublethal x-ray damage in HeLa S-$3_{oxf.}$ cells exposed to a nonlethal concentration of methotrexate added to the medium at the time of plating. The first x-ray dose was given 18 hours after plating, and the drug was removed from the medium 24 hours after plating.

two doses of 200 rads, compared with the fraction surviving a single dose of 400 rads at the same times after plating and after the addition of the drug to the growth medium. This is shown in Figure 8. If the first x-ray dose was delivered more than 16 hours after the addition of the drug to the medium, however, no early recovery was seen. As is shown in Figure 9, the fraction of cells surviving two doses of 200 rads was *lower* than that after a single dose of 400 rads delivered 18 hours after the addition of MTX to the plating medium because of the additional cell-killing produced by longer incubation in the presence of the drug by the time the second x-ray dose was received. This loss of recovery from sublethal x-ray damage was also impermanent; by 24 hours after the removal of MTX from the medium, HeLa cells again showed the ability to recover between fractionated doses of 400 rads delivered 0–6 hours apart, although the magnitude of this recovery may be slightly smaller than that seen in cells unexposed to the drug but irradiated at the same time after plating. This is shown in Figure 10.

DISCUSSION

In bacteria[3] and in mammalian cells,[18] a deficiency in the metabolic availability of the DNA precursor, thymidine, results in a state of 'unbalanced growth' which is characterized by rapid cessation of progress through the cell cycle. Mitosis and DNA synthesis are blocked, although RNA and protein synthesis continue. Methotrexate, an analogue of folic acid, inhibits thymidine incorporation into DNA by eliminating the synthesis of the necessary folate-

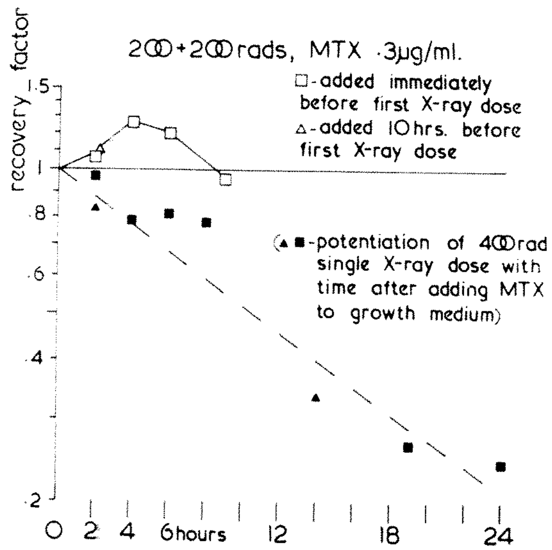

Fig. 8. Early recovery and change in response to single x-ray doses in HeLa S-$3_{oxf.}$ cells with time after the addition of a high (cell-killing) concentration of methotrexate to the medium. The drug was added 18 hours after plating and removed 24 hours later. The first 200 rad x-ray dose for the recovery studies was given immediately after addition of the drug (open squares) or 10 hours after the addition of the drug (open triangle). Single x-ray doses of 300 rads were given 2–24 hours after the addition of the drug to the medium (closed squares and triangle) at times comparable to the second dose in the divided-dose recovery experiment.

containing co-enzymes,[17] and has been shown to produce a state of 'unbalanced' growth in several strains of mammalian cells in culture.[8,15,18] The reversal of the methotrexate block, either by the addition of thymidine-containing growth medium[18] or by the addition of leucovorin (folinic acid)[8] to cells in culture produces a degree of synchrony in the subsequent progression of these cells through the division cycle. These findings provide a possible explanation for the results obtained in combination of methotrexate with x-irradiation.

(1) Concentrations of methotrexate which on 24 hour exposure did not prove lethal to HeLa cells sensitized those cells to the effects of x-irradiation, but did not alter the capacity of those cells to recover from the sublethal damage done to them by irradiation, and did not alter the oxygen enhancement ratio for single x-ray doses delivered under oxygenated and anoxic conditions. At these low drug concentrations, true potentiation of the radiation response was seen, but unbalanced growth probably did not occur and no significant synchrony was induced in the progession of these cells through the cell cycle after the removal of the drug from the medium. The highest nonlethal methotrexate concentration was equal to a dose of 2.1 mg. uniformly distributed throughout the body of a 70 kg. patient.

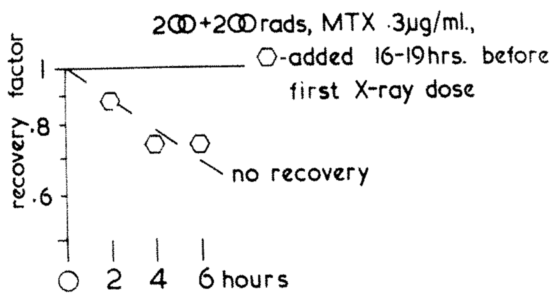

Fig. 9. Failure of early recovery in HeLa S-3_{oxf}. cells exposed to a high (cell-killing) concentration of methotrexate for over 16 hours prior to the first 200 rad x-ray dose. Dividing the irradiation into two equal fractions spaced apart by 2–6 hours did not result in an increase in the fraction of cells surviving to form clones.

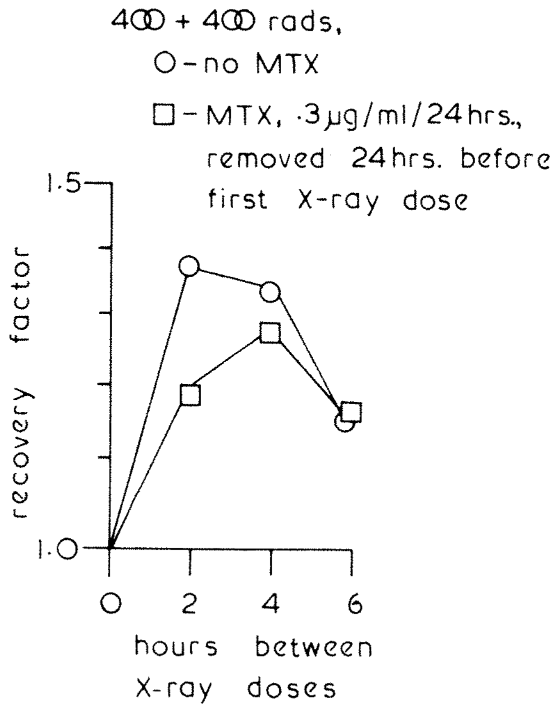

Fig. 10. The open squares show the pattern of early recovery in HeLa S-3_{oxf}. cells given their first x-ray dose 48 hours after plating, 24 hours after the removal of methotrexate, 0.3 µg/ml., which had been added to the medium at the time of plating. The open circles show the recovery obtained in the same experiment in cells not exposed to methotrexate but also given their first x-ray dose 48 hours after plating.

(2) Concentrations of methotrexate which *did* kill cells did so only when those cells were synthesizing DNA (cf. Figure 2), and those cells which survived incubation in medium containing high concentrations of methotrexate (equivalent to 21 mg. in a 70 kg. patient) were those which failed to attempt DNA synthesis during the time the drug was present. The cell population thus selected by methotrexate had an x-ray dose-response for cell reproductive survival which was characterized by a markedly reduced 'shoulder' region, and failed to recover from sublethal radiation damage as measured by comparison of two-dose survival with that after single irradiation. In addition, this selected population showed a markedly reduced oxygen enhancement ratio for single x-ray doses de-

livered under oxygenated and anoxic conditions.

By using extremely rigorous techniques to exclude contamination of a synchronized cell population by small numbers of cells in other phases of the cycle, it has been shown that there are dramatic variations in both the slope of the radiation dose-response curve for Chinese hamster cells, and in the size of the shoulder region of the curve, depending upon the point in the division cycle at which the cells are irradiated.[19] The pattern of change in radiosensitivity through the cell cycle in Chinese hamster and HeLa cells now appears to be similar when equally rigorous techniques are used to ensure 'pure' populations in each phase of the division cycle.[9] Therefore, applying the more extensive data for Chinese hamster cells to the present situation, it seems reasonable to assume that the absence of recovery in the methotrexate-selected cell population, and perhaps also the reduction in oxygen enhancement ratio, may be due to nothing more than the production of a synchronous population of HeLa cells by methotrexate exposure. This surmise is reinforced by the observation that 24 hours after the removal of methotrexate from the medium, the surviving cells show a radiosensitivity, capacity for recovery, and oxygen enhancement ratio essentially the same as that in a population of HeLa cells never exposed to the effects of the drug. These effects should not be expected to be unique to methotrexate; any other drug capable of producing sufficient synchrony in a population of mammalian cells might yield selected populations equally devoid of capacity for recovery from sublethal damage, and with a similarly reduced protection factor for the irradiation of anoxic cells.

How can these ideas be applied to clinical radiotherapy, to maximize tumor destruction and minimize additional damage to normal tissues? The application of laboratory findings in single-cell systems to the complex problem of clinical radiotherapy is always hazardous, but the following thoughts suggest themselves for clinical consideration:

(1) It is probably of little value to give single large doses of methotrexate, as has been done in some clinical studies, because of the vastly increased amount of the drug which patients appear to tolerate. Only those cells actively synthesizing DNA during the relatively brief persistence of the drug in the circulation will be affected by it, and smaller single doses of the drug may well kill quite as many tumor cells. Repeated smaller doses of the drug should, in fact, kill *more* tumor cells.

(2) The sequential use of methotrexate followed by x-irradiation should require little change in either the total x-ray dose which can be given, or the pattern of dose-fractionation. By 24 hours after the removal of even high concentrations of the drug from their environment, surviving tumor cells showed both radiosensitivity and capacity for recovery which were unchanged from those of cells never exposed to the effects of the drug.

(3) A great potential value in using methotrexate in combination with radiotherapy lies in reducing the degree of protection afforded to tumor cells by local hypoxia at the time of irradiation. Since a reduction in oxygen enhancement ratio for subsequent x-irradiation is only obtained after exposure to concentrations of the drug which are lethal to some cells (probably due to the induction of some synchrony in the surviving population), the largest tolerated dose of methotrexate should be given in such a way as to maintain a high concentration of the drug in the circulation for at least 24 hours, and an x-ray dose given at the end of this period. Individual x-ray doses should be as large as possible, so that not only are all the well-oxygenated tumor cells in the radiation field eliminated, but the greatest use is also made of any increased killing of hypoxic tumor cells.

(4) The total number of x-ray doses given should probably be minimized for concomitant use of methotrexate and

fractionated radiotherapy. Daily doses of methotrexate plus a large number of fractionated x-ray doses (*e.g.* daily treatment over 4–5 weeks) may result in an unexpectedly great effect on both tumor *and* normal tissues, due to failure of recovery between the fractionated radiation doses. This complication has already been rereported in at least one clinical study.[6]

(5) A significant advantage is likely to be seen in the combination of methotrexate and radiotherapy *only* in those tumors in which the primary clinical problem is the failure to eradicate all disease in the primary site or in treated metastatic sites. Those types of tumor in which the disease which eventually kills the patient is probably never treated, due to unrecognized (even microscopic) metastases present at the time of treatment of the primary tumor by radiotherapy, should preferably be excluded from clinical trials of the drug-radiation combination. These latter types of tumors, or rather the patients who bear them, should only be used in the evaluation of effects of methotrexate and radiation in combination upon normal tissues unavoidably included in the radiation field.

(6) The pattern of combined therapy which seems most likely to achieve success uses the minimum number of radiation dose fractions which is compatible with local radiotherapeutic experience. Each radiation dose is preceded by a short course (24–48 hours) of the highest tolerated dose of methotrexate, administered orally at relatively frequent intervals (*e.g.* every 6 hours). After each radiation treatment, no further drug is administered until the appropriate time before the next radiation dose. A random series prospective trial comparing this regime (using one radiation treatment per week for 6 weeks) with a similar course of radiotherapy, either without the drug or concurrently with the continuous daily administration of methotrexate at the necessarily lower maximum-tolerated dose level, is underway using patients with locally-advanced carcinomata of the cervix and bladder in the Radiotherapy Department in Oxford.

SUMMARY

The lethal effects of *methotrexate* upon human tumor cells *in vitro* depend not only upon the concentration of the drug around those cells, but also upon the length of time for which the drug and the cells remain in contact. Short-term exposure to even very high concentrations of methotrexate may leave a large proportion of tumor cells intact, while longer exposures to lower drug concentrations will leave few cells capable of repeated divisions.

Exposure of human tumor cells to concentrations of methotrexate which are nonlethal nonetheless sensitizes those cells to subsequent x-irradiation. Tumor cells which survive exposure to higher, cell-killing concentrations of methotrexate are protected less by anoxia than untreated cells when they are irradiated immediately afterwards.

When irradiated immediately after exposure to the drug, methotrexate-treated cells show no recovery from sublethal x-ray damage; if irradiated 24 hours or more after their removal from methotrexate, those tumor cells which have survived are capable of recovery between fractionated x-ray doses and show no reduction in anoxic protection.

These results in a relatively simple single-cell system are examined in the context of treatment schemes used in the several published clinical studies of radiotherapy combined with methotrexate chemotherapy. A plan is proposed for the optimum combination of these two agents.

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THE TREATMENT OF CARCINOMA OF THE BLADDER WITH SPECIAL REFERENCE TO THE USE OF PREOPERATIVE RADIATION THERAPY COMBINED WITH 5-FLUOROURACIL*

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PRIOR to the use of megavoltage radiation therapy, the treatment of bladder carcinoma with conventional x-ray therapy was most disappointing. If adequate tumor doses were given, the patient usually had skin reactions, urgency, frequency, reduced bladder capacity, severe fibrosis in some cases, and often telangiectasis of the bladder mucosa.

Since cobalt 60 teletherapy became available (1951), there has been a renewed interest in the treatment of bladder carcinoma utilizing megavoltage radiation therapy.

The advantages of megavoltage therapy are particularly apparent in the treatment of a tumor in this anatomic location with its surrounding bony structures and its close proximity to the small bowel and rectum. The major disadvantages of conventional x-ray therapy are the high absorption of the energy by the skin, the higher absorption by the bone than in the surrounding soft tissues, and the side and back scatter which occurs when energies in this range are used. Most of these effects are eliminated or reduced when megavoltage equipment, such as the 1 and 2 million volt General Electric resonant generators, the 2 million volt Van de Graaff electrostatic generator, the cobalt 60 teletherapy units, the 4 to 8 mev. linear accelerators, and the betatrons are utilized.

Better antibiotics, improved anesthesia and surgical techniques, the more careful staging of the disease, and the team approach have all been of decided value in the management of patients afflicted with this disease.

Protocol studies attempting to evaluate combinations of therapy, surgery versus irradiation, surgery plus irradiation, and irradiation plus surgery and chemotherapy, have been most helpful in the endeavor to understand better this disease and to improve the end results of treatment.

STAGING OF BLADDER TUMORS

	Marshall-Jewett Classification
Superficial tumor confined to mucosa	O
Tumor confined to submucosa	A
Tumor half-way through the bladder muscle	B_1
Tumor more than half-way through the bladder muscle	B_2
Tumor extending to perivesical fat	C
Tumor spread to regional lymph nodes	D_1
Tumor spread to distant sites	D_2

HISTORICAL REVIEW

Eisenberg and Heise[6] reported on 12,239 white patients with bladder cancer from data collected from the California, Connecticut, and Massachusetts central tumor registries between 1940 and 1959. The ratio of males to females was 2.5 to 1. Approximately 5.5 per cent of cancers occurring in men and 2 per cent occurring in

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women originate in the bladder. They found that from 1940 to 1959 men experienced a rise in the 5 year survival rate from 42 to 52 per cent. The corresponding rate for women increased from 36 to 55 per cent. They found no evidence to indicate that future results will improve, unless there are significant changes in treatment methods.

Baker[1] has found the incidence of pelvic lymph node involvement to be related to the extent of involvement of the bladder wall. He noted that when the tumor extends to the superficial muscle layer the lymph nodes are involved in 1 out of 5 cases. When the tumor cells extend deeply into the muscle layer, in 8 of 10 cases there is lymph node involvement.

Wallace[15] in commenting upon the factors influencing the prognosis of early cancer of the bladder, stated that the two main factors in prognosis are the surface extent of the disease, and the stage or depth of infiltration of the tumor cells. He believes that the basement membrane is probably the greatest single factor in prognosis and that when the membrane has been ruptured, even to a slight extent, the mortality increases by 20 per cent. When extension into the submucosa of the bladder occurs, there is a further increase of 20 per cent in the mortality. If the deep muscle or perivesical tissues are penetrated, the incidence of positive lymph nodes increases rapidly to over 50 per cent.

It is remarkable how well the bladder is able to tolerate large doses of radiation, such as are given, for example, in the treatment of carcinoma of the cervix. During the course of radiation therapy the bladder frequently sustains considerable reaction but it has the capacity to re-epithelialize denuded areas of the lining epithelium satisfactorily, when the patient is given bladder sedatives and antibiotics and appropriate rest. Many patients with cancer of the cervix have been cured by radiation therapy and I know of no reports to indicate that bladder carcinoma is more frequent in this group than in non-irradiated women or that a significant number of permanent bladder complications have occurred.

It is difficult to predict the response of a bladder tumor to irradiation strictly on the basis of histopathology. In general, the anaplastic infiltrating tumors are more radiosensitive. Any bladder infection which occurs during radiation therapy should be immediately and adequately treated to prevent the occurrence of sequelae. When infection is present bacterial studies of the urine should be made. If the patient has had previous fulgurations or bladder surgery, the radiation reactions are usually more prominent.

Prior to the institution of radiation therapy the carcinoma should be staged. The staging is based upon cystoscopic examination, bimanual examination under anesthesia, biopsy, cystography and intravenous urography. Alkaline phosphatase, renal function, creatinine, complete blood cell count, and urinalysis are also done.

Morrison and Deeley[12] in evaluating the transitional cell tumor response at one year according to dose given, stated that an increase in dose (for example, from 5,000 to 6,000 rads tumor dose) may not produce a greater disappearance rate of the primary lesion, and that there may be an optimum tumor dose; also, that different methods of fractionation should be investigated.

DeWeerd and Colby[4] carried out a planned program of combined radiation therapy and total or partial cystectomy and pelvic lymphadenectomy for bladder carcinoma. The majority of the lesions were Grade III (Broders) and Stages B_1B_2, and C (Marshall-Jewett) transitional cell carcinoma.

The patients were divided into two groups. The Group I series included 27 patients. Cobalt 60 teletherapy or 6 mev. linear accelerator x-ray therapy was used. The treatment was directed to the bladder and adjacent pelvic lymph nodes. The total tumor dose was approximately 4,800 rads given in 2 sessions. Both sessions were

of 12 to 14 days duration with a rest period of 3 weeks between sessions. Approximately 6 weeks after completion of the radiation therapy the patients were re-evaluated and a total or segmental cystectomy and partial pelvic lymphadenectomy were done.

Group II included 7 patients. These patients were given a total tumor dose of from 1,800 to 2,400 rads delivered during 3 consecutive days. A total or segmental cystectomy and partial pelvic lymphadenectomy were done immediately after the radiation therapy was completed. No residual intact carcinoma cells could be found in 9 surgical specimens from the Group I patients (33 per cent of the cases). Postoperative complications, morbidity, and mortality have not been increased. Follow-up examinations of the patients have not been carried out long enough to enable them to assess the results.

Some of the difficulties in the treatment of bladder cancer are the inability to evaluate effectively the intrinsic nature of the tumor in each patient, the multiplicity of foci of origin, the diffuseness of the lesions and their ability to metastasize early to regional lymph nodes. There is also a wide variation in the radiation sensitivity of bladder tumors. The degree of radiosensitivity cannot be determined prior to treatment.

Brice[2] reported on the 10 year follow-up of 230 consecutive cases of radical total cystectomy which had been performed between June 24, 1948, and February 29, 1955, for which a 5 year report had been made by Whitmore and Marshall in 1962.[16] Bilateral pelvic lymphadenectomy was performed in all cases, and removal of the rectum in 67 of the 230 patients. There were 32 postoperative deaths, or 14 per cent.

Of 23 of the 230 patients who had Stage B_2 cancer, 4 patients (17 per cent) survived 5 years; 53 patients had Stage C and 7 (13 per cent) of these lived 5 or more years. Of 76 patients who had bladder cancer Stages B_2 and C without demonstrable metastases or local extension, 11 (14 per cent) lived 5 years. No patient with D_1 cancer lived for 10 years. Of 35 patients with lesions Stage O_1, A_1, or B_1, 47 per cent survived for 5 years, and 6.6 per cent for 10 years.

Veenema *et al.*,[14] have used ThioTEPA systemically or topically, alone or in combinations with radiotherapy, and have found that it produced very little effect on invasive or advanced disseminated bladder tumors. When ThioTEPA is used topically, partial destruction of the surface lesion does occur in some cases. They reported that when ThioTEPA was used topically, 38 of 57 patients who had superficial, small, well-differentiated papillary tumors had encouraging results. Sixty milligrams of ThioTEPA was dissolved in 30 to 60 cc. of distilled water and instilled in the bladder and allowed to remain for 2 hours. Four instillations constitute a course, with an instillation given at weekly intervals. Thirteen of the 38 patients had complete destruction of the tumors. There was no effect in 11 patients. They plan to continue the use of ThioTEPA for prophylactic use in patients who have had recurrent superficial bladder tumors.

Einhorn *et al.*,[5] are of the opinion that if adequate doses of radioactive materials are given intravesically, there is a major risk of hematuria, contraction of the bladder, ureteral insufficiency with vesicoureteral reflux, reduced resistance to urinary tract infection, and impaired healing.

Mackenzie *et al.*,[11] reporting on their experience with supervoltage x-ray therapy in the treatment of bladder cancer stated that the 2 to 3 year survival rates for patients treated by radical surgery or supervoltage radiation therapy are quite similar, especially in view of the unfavorable factors of selection in the radiation therapy series. For example, for radical surgery for patients with bladder carcinoma staged B_2 and C, the 2 and 3 year survival rates were 33 per cent and 22 per cent; for those similarly staged and treated by mega-

voltage radiation therapy, 30 per cent and 20 per cent. The results were better for those who had preoperative irradiation and radical cystectomy (42 per cent). They believe that radiation therapy followed by radical cystectomy offers the greatest hope for patients with the earlier infiltrated stages.

Whitmore *et al.*,[17] reported in 1963 on the results of preoperative radiation therapy given to 50 patients with bladder carcinoma treated from 1959 through 1962. Megavoltage equipment was used and the majority (42 patients) received 4,000 rads tumor dose given in 4 to 6 weeks. The complication rate was higher than in the non-irradiated group who had radical cystectomy alone (62 per cent versus 51 per cent). There was no definite increase in mortality. Nine of the 50 patients or 18 per cent had no cancer in the operative specimens, and an additional 8 had carcinoma *in situ* only.

Crigler and associates[3] reported the results of radiation therapy used either alone or subsequent to various surgical procedures in 352 cases of bladder cancer. The patients were treated largely with 22 mev. x-rays or cobalt 60 gamma rays between 1954 and 1962. The major complication rate was 13 per cent and the mortality rate 5 per cent. The crude survival rate for the whole series is 31 per cent at 3 years, and 20 per cent at 5 years. The corresponding figures for stages B_2 and C are 44 and 28 per cent. Since 1962, they have done preoperative irradiation followed by simple total cystectomy and bilateral uretero-ileostomy as the routine policy of treatment for patients with lesions in stages B_2 and C.

Poole-Wilson[13] has used 500 kv. x-ray therapy equipment and delivered from 5,000 to 6,000 r in 3 to 5 weeks to 64 patients with gross infiltrating bladder carcinoma, with a 5 year survival of 25 per cent. A palliative tumor dose of 3,000 r was given to 48 patients in 8 days with 6 per cent of the patients surviving for 5 years. His experience using a central source of cobalt 60 for intracavitary irradiation has been disappointing.

Of 38 patients staged A to C treated at the University of California (San Francisco),[5] 8 (22 per cent) have lived more than 3 years without evidence of disease and with normal bladder function. Of 23 patients treated more than 5 years ago, 8 were alive after 5 years (35 per cent) and 4 (17 per cent) were controlled by irradiation alone, with normal bladder function. The radiation therapy tumor doses ranged from 5,000 r in $5\frac{1}{2}$ weeks to 6,000 r in 7 weeks. Cobalt 60 or 1 mev. x-ray therapy equipment was used.

It is quite possible that megavoltage therapy given before extensive surgical procedures have been carried out, or before numerous fulgurations have been done, will improve the end results both for cure and for palliation.

MATERIAL AND METHOD

During the past several years, there has been a trend to use combined treatment, and, in particular, megavoltage therapy and antitumor drugs as parts of the definitive and curative cancer therapeutic regimen. The reason has been because of the appreciation of the limitations of our present methods of therapy and also because of improved equipment, techniques, and the new antitumor drugs which have become available. The discovery of new chemotherapeutic agents has provided another avenue of approach to the problem.

In general, tumor tissue is more susceptible to damage than normal tissue when ionizing radiation is employed. The use of any agents or combination of agents or treatment modalities which will increase the sensitivity of tumor cells or increase the resistance of normal cells could improve the end results of treatment.

Of the more than 20 chemotherapeutic drugs currently in clinical use in the treatment of bladder cancer, the only one which appears to be promising when used systemically is 5-Fluorouracil (5-FU). When this drug is used alone, it is not cura-

tive for bladder cancer or for any other type of cancer. It acts as an antimetabolite. It interferes with the synthesis of thymine from uracil, with the production of less nucleic acids.

Patients receiving 5-FU combined with radiation therapy in the treatment of bladder cancer have had a much greater response than one would normally anticipate. The combined effect of the two agents (chemotherapy and radiation) is greater than the simple addition of the effect of each agent when used alone.

It did not take long to find out that if a complete course of preoperative radiation therapy is given (6,000 rads) and then surgery is carried out 4 to 8 weeks later, the morbidity and probably the mortality are increased without any improvement in the 5 year survival rates.

Also, if one attempts to give a full course of 5-FU (with the recommended dosage when this drug is used alone) combined with a full course of radiation therapy, the morbidity will be excessive and the treatment will have to be interrupted or discontinued in many cases because of the resultant toxicity.

The following protocol is employed at the present time by the Division of Urology and the Division of Radiation Therapy at UCLA for the treatment of carcinoma of the bladder, primarily as adjuvants to definitive open surgery (cystectomy or partial cystectomy). Since this form of combined treatment has been used, complete tumor disappearance in a relatively higher per cent of patients whose original tumors were still confined to the bladder has been noted. A number of the patients who have refused cystectomy are being followed by periodic cystoscopy and biopsy. Excellent responses have been observed in cases with multiple superficial, but rapidly recurring, tumors of low histologic grade as well as in highly undifferentiated tumors with deep muscle invasion. It is doubtful whether large tumors showing perivesical extension and fixation or local lymph node spread will respond to this method of treatment.

The patient is given 5-FU* by continuous intravenous infusion. One ampoule of 500 mg. of 5-FU is dissolved in 1,000 cc. of 5 per cent glucose and water to which is added 10 mg. of heparin and 10 mg. of hydrocortisone. The latter two drugs are used to minimize phlebitis during the week or two when the continuous intravenous infusions are given. Plastic catheters are used for the intravenous infusions. The 1,000 cc. mixture is given over 12 hours and repeated during the next 12 hours so that the patient receives 1 gram of 5-FU per day. Every attempt is made to continue this intravenous therapy over a period of 8 days and, if possible, for 14 days. Concomitantly with the 5-FU the patient is given cobalt 60 teletherapy and receives an average of 200 rads tumor dose daily. By the time he leaves the hospital, the patient will have received between 1,600 and 2,400 rads tumor dose. After leaving the hospital he is continued on cobalt therapy, usually 6 days a week, until a tumor dose of 3,500 rads has been reached. During the time that he is receiving cobalt 60 teletherapy as an outpatient, he receives an infusion of 500 cc. of 5 per cent glucose in water to which is added 1 ampoule (500 mg.) of 5-FU. The infusion is made over a period of approximately 2 hours. This is done every other day. Occasionally toxicity is encountered with this infusion, even though the amount of the drug being administered is smaller than that which the patient received in the hospital. Toxicity usually consists of diarrhea and nausea and more rarely leukopenia or platelet depression. The white blood cell count and platelets are checked every day while the patient is on inpatient therapy and when he becomes an outpatient these determinations are made before he receives the 5-FU. If the white blood cell count falls below 5,000 or the platelet count below 100,000, treatment is interrupted temporarily until the count re-

* 5 Fluorouracil-Roche.

turns to more normal levels. Following the completion of combined therapy it is customary to wait 1 month before performing cystoscopy and repeat biopsy. If cystectomy is decided upon it should be done between 4 weeks and 8 weeks after the completion of combined therapy.

It is not believed that there is any advantage to giving the 5-FU undiluted, intravenously. It is not considered necessary to give the drug to toxicity in order to obtain better results. Hall and associates,[7] in commenting upon the time and vehicle studies of a safe and effective method for administering 5-FU, found in a study of 87 patients with breast cancer that the overall response rate of 25 per cent was not related to the time of infusion or vehicle, and that the beneficial effect was not dependent upon the production of systemic drug toxicity.

RESULTS

The experience at UCLA using combined radiation therapy, chemotherapy, and surgery (in most cases) is shown in Tables I to VI inclusive. In the beginning only small doses of 5-FU were given. At the present time a course of 5-FU consists of from 13 to 15 or more grams. Some of the patients included in this series have been previously reported;[9,10] however, the present status of all the cases is given in this report.

Patients receiving 5-FU combined with radiation therapy in bladder cancer have had a much better clinical response than one would expect. The combined effect of the two agents (chemotherapy and radiation therapy) is greater than that of each agent when used alone. It is difficult to explain the absence of tumor cells in a high percentage of potentially curable blad-

TABLE I

PREOPERATIVE IRRADIATION, CHEMOTHERAPY AND SURGERY FOR BLADDER CANCER

Stage A

Patient	Sex	Age	Cell Type	Grade	5-FU (gm.)	Tumor Dose Cobalt 60	Surgery	Result	Present Status
HJ	M	67	T.C.	III	5.0	3,389 rads	Cystectomy	Partial regression	Alive—no tumor 31 months
WG	M	66	T.C.	III	5.9	3,000 rads	Cystectomy	No tumor	Alive—no tumor 43 months
SC	M	62	T.C.	II	15.0	3,483 rads	Transurethral resection	No tumor	Alive—no tumor 19 months
HR	M	71	T.C.	III	3.0	2,100 rads	Transurethral resection; partial cystectomy	None	Deceased 24 months
EK	M	54	T.C.	III	11.0	3,785 rads	Cystectomy	No tumor	Alive—no tumor 18 months
AN	F	48	T.C.	II	10.0	3,360 rads	None	No tumor	Alive—no tumor 10 months
WF	M	32	T.C.	II	14.0	3,500 rads	Cystectomy	No tumor	Alive—no tumor 10 months
NM	F	76	T.C.	II	13.0	3,555 rads	None	No tumor	Alive—no tumor 12 months
GG	M	64	T.C.	II	15.0	3,500 rads	Cystectomy	No tumor	Alive—no tumor 6 months

T.C. = transitional cell carcinoma.

TABLE II

PREOPERATIVE IRRADIATION, CHEMOTHERAPY AND SURGERY FOR BLADDER CANCER

Stage B1

Patient	Sex	Age	Cell Type	Grade	5-FU (gm.)	Tumor Dose Cobalt 60	Surgery	Result	Present Status	Comments
RM	M	68	T.C.	II	3.5	3,075 rads	Cystectomy	No tumor	Alive—no tumor 44 months	
RB	M	45	T.C.	II	5.2	3,406 rads	Partial cystectomy	Foci of tumor	Alive—no tumor 29 months	
LM	M	50	T.C.	II	4.0	3,114 rads	Cystectomy	No tumor	Alive—no tumor 32 months	
JSJ	M	68	T.C.	II	3.6	3,050 rads	Transurethral resection	Biopsy negative	Alive—no tumor 27 months, lost to follow-up	One small superficial recurrence at 12 months; transurethral resection—no recurrence
JS	M	64	T.C.	III	2.8	3,600 rads	None	No tumor	Alive—no tumor 36 months	Cystectomy 22 months after first treatment for recurrence; alive—no tumor 12 months after surgery
CN	M	66	T.C.	IV	3.5 2 months later 12 months later 15.0	4,606 rads 1,605 rads	Fulguration	None	Deceased 36 months	Cystectomy 24 months after first treatment for recurrence; deceased 12 months after surgery with bone metastases
SL	M	76	T.C.	III	5.0	6,120 rads	None	Biopsy negative	Deceased 56 months	No tumor at death from cerebral vascular accident
GS	M	67	T.C.	II	4.5	3,620 rads	Cystectomy	No tumor	Alive—no tumor 36 months	
JSR	M	66	Epid.	IV	14.0	3,363 rads	Cystectomy	No tumor	Alive—no tumor 22 months	
GK	M	57	T.C.	III	3.5	3,440 rads	Cystectomy	Partial regression	Alive—no tumor 37 months	
IG	F	67	Sq.	III	3.5	3,009 rads	None	No cystectomy	Alive—no tumor 19 months	Lost to follow-up
FM	M	59	T.C.	IV	3.8	3,500 rads	Cystectomy	Partial regression	Deceased 22 months	Ureteral recurrence 22 months
LE	M	76	T.C.	IV	4.6	4,000 rads	None	None	Alive—with tumor 14 months	Lost to follow-up
WE	M	54	T.C.	III	9.0	3,507 rads	Cystectomy	Partial regression	Alive—no tumor 14 months	
BR	M	61	T.C.	III	9.0	3,171 rads	None	Marked regression	Deceased 12 months	Cystectomy for recurrence 12 months after first treatment; postoperative death

T.C. = transitional cell carcinoma; Epid. = epidermoid carcinoma; Sq. = squamous cell carcinoma.

Table III

PREOPERATIVE IRRADIATION, CHEMOTHERAPY AND SURGERY FOR BLADDER CANCER

Stage B_2

Patient	Sex	Age	Cell Type	Grade	5-FU (gm.)	Tumor Dose Cobalt 60	Surgery	Result	Present Status	Comments
TD	M	64	T.C.	II	3.0	2,057 rads	Cystectomy	No tumor	Deceased 25 months	
CS	F	69	T.C.	II	3.5	3,908 rads	Cystectomy	No tumor	Deceased 37 months	Distant tumor spread
JP	M	50	T.C.	III	5.0	3,149 rads	Cystectomy	Partial regression	Alive—no tumor 47 months	
ES	M	59	Sq.	II	3.5	3,522 rads	Cystectomy	No tumor	Alive—no tumor 36 months	
JM	M	42	T.C.	IV	6.5	5,025 rads	None	No tumor	Alive—no tumor 62 months	Negative cytoscopy
EB	F	50	T.C.	III	3.6 1,956 rads 2nd course 8 months later 2.6 4,013 rads		None	No tumor	Suicide 43 months	Recurrence 8 months after first treatment No tumor 30 months after last treatment
CP	M	72	T.C.	I	5.5	5,005 rads	None	Marked relief of symptoms; no cytoscopy	Deceased 47 months	Symptoms at 38 months after treatment; bladder fixed—transurethral resection for symptom relief
CG	M	64	T.C.	III	5.5	5,723 rads	None	No tumor	Alive—no tumor 47 months	
CA	M	55	T.C.	III	15.0	3,500 rads	Cystectomy	Partial regression	Alive—no tumor 8 months	
FM	M	58	T.C.	III	13.5	3,472 rads	Cystectomy	Partial regression	Alive—no tumor 12 months	
MP	M	45	T.C.	III	11.0	3,450 rads	Cystectomy	Partial regression	Alive—no tumor 12 months	

T.C. = transitional cell carcinoma; Sq. = squamous cell carcinoma.

Table IV

PREOPERATIVE IRRADIATION, CHEMOTHERAPY AND SURGERY FOR BLADDER CANCER

Stage C

Patient	Sex	Age	Cell Type	Grade	5-FU (gm.)	Tumor Dose Cobalt 60	Surgery	Result	Present Status	Comments
AC	M	70	Sq.	II	3.5	2,104 rads	Cystectomy	Partial regression	Alive—no tumor 59 months	
JJ	M	59	Epid.	III	4.0	3,585 rads	Cystectomy	None	Deceased 8 months	Developed vesicocolon fistula 6 months postoperative
LC	F	54	T.C.	II	4.7	4,189 rads	Cystectomy	Partial regression	Deceased 9 months	Cerebral vascular accident
MS	M	60	T.C.	III	4.0	3,399 rads	Cystectomy	Partial regression	Deceased 17 months	Pelvic recurrence at 11 months; 40 per cent subjective improvement
ML	M	52	T.C.	III	15.0	3,500 rads	Cystectomy	Partial regression	Alive—no tumor 6 months	
FVE	F	70	T.C.	IV	15.0	3,500 rads	None	No tumor	Alive—no tumor 15 months	Cystectomy for recurrence at 16 months; alive—no tumor

Sq. = squamous cell carcinoma; Epid. = epidermoid carcinoma;
T.C. = transitional cell carcinoma.

TABLE V

PREOPERATIVE IRRADIATION, CHEMOTHERAPY AND SURGERY FOR BLADDER CANCER

Stage D_1

Patient	Sex	Age	Cell Type	Grade	5-FU (gm.)	Tumor Dose Cobalt 60	Surgery	Result	Present Status	Comments
FD	M	72	T.C.	II	6.5 16 months later 15.0	5,814 rads	None	Negative cystoscopy; lost to follow-up	Alive with tumor 24 months	Recurrence 16 months
AL	M	46	T.C.	II	4.6 9 months later 15.0	4,000 rads	None	None	Deceased 10 months	Lymphedema; vesico-colon fistula
VG	M	60	Sq.	III	5.5	4,500 rads	Transurethral resection	Partial regression	Deceased 6 months	Uremia; widespread metastases
NG	M	53	T.C.	II	3.0	6,178 rads	Exploratory laparotomy	40–50 per cent regression	Deceased 18 months	Metastases to spine
ML	F	55	T.C.	III	postoperative 5.2	6,099 rads	Cystectomy	Partial regression	Deceased 36 months	Azotemia
DT	M	63	T.C.	II	3.5	5,025 rads	Partial cystectomy	Partial regression	Deceased 12 months	Previous irradiation
JW	M	50	T.C.	II	2.5	2,204 rads	Cystectomy	Partial regression	Alive with tumor 56 months	Urethrectomy at 43 months
TH	M	46	T.C.	III	3.2	4,080 rads	None	None	Deceased 8 months	Previous irradiation
JA	F	56	T.C.	III	18.0	3,450 rads	Cystectomy	None	Deceased 8 months	
TG	M	44	T.C.	IV	9.5	3,580 rads	Exploratory laparotomy and Bricker operation	None	Deceased 8 months	
MB	M	56	T.C.	II	13.0	3,594 rads	Exploratory laparotomy and Bricker operation	None	Deceased 6 months	
DC	M	59	T.C.	III	12.0	3,538 rads	Cystectomy	Partial regression	Deceased 6 months	
EL	F	65	T.C.	III	13.0	3,327 rads	Cystectomy	No residual tumor in bladder	Alive—no tumor 12 months	
LW	M	53	T.C.	IV	14.25	3,471 rads	Cystectomy	None	Deceased 6 months	
JF	F	45	T.C.	III	3.8 36 months later 5.1	2,100 rads 4,233 rads	Cystectomy	Partial regression	Alive with tumor 46 months; lost to follow-up	Recurrent iliac lymph nodes and inferior vena cava obstruction at 36 months; lymph node negative
IR	F	48	T.C.	IV	Initial 4.5 Postoperative 2.0 12 months later 15.0 6 months later 15.0	 3,372 rads 3,084 rads — —	Cystectomy	90 per cent regression	Deceased with tumor 30 months	Recurrence at 13 months; 5-FU, subjective improvement, no objective improvement
BE	M	67	T.C.	III	4.7 3 months later 1.0	3,021 rads 913 rads	Exploratory laparotomy	None	Deceased 7 months	Widespread disease
RG	F	78	Sq.	II	2.5	2,311 rads	Partial regression	Partial regression	Deceased 12 months with disease	Abdominal fistula with tumor
RP	M	69	T.C.	III	5.5 12 months later 15.0 6 months later 4.0	3,500 rads 3,000 rads 2,256 rads	Cystectomy	Partial regression	Deceased 22 months	

T.C. = transitional cell carcinoma; Sq. = squamous cell carcinoma.

Table VI

PREOPERATIVE IRRADIATION, CHEMOTHERAPY AND SURGERY FOR BLADDER CANCER

Stage D_2

Patient	Sex	Age	Cell Type	Grade	5-FU (gm.)	Tumor Dose Cobalt 60	Surgery	Result	Present Status	Comments
AL	M	49	T.C.	III	6.5	5,066 rads	None	None	Deceased 3 months	
OM	M	44	T.C.	IV	4.1 2 months later 4.0	3,066 rads 3,086 rads	Exploratory laparotomy at 3,066 rads	Partial regression	Deceased 16 months	Did well for 7 months post-operative
FS	M	60	T.C.	III	2.5 postoperative 4.0	3,345 rads 2,787 rads	Exploratory laparotomy	None	Alive with tumor 14 months	
PL	M	63	T.C.	III	4.5	5,050 rads	None	None	Deceased 9 months	
CA	M	70	T.C.	III	4.9 6 months, later 7.0	3,530 rads 4,000 rads	None	None	Alive with tumor 22 months; lost to follow-up	
LG	M	54	T.C.	III	4.0 12 months later 15.0	5,100 rads	10 years post-cystectomy urethrectomy done	Complete regression of metastatic lymph node	Deceased 22 months	Developed pulmonary metastasis 20 months later
JA	M	69	T.C.	IV	8.5	1,845 rads	None	Pain response	Deceased 12 months	
JI	M	76	T.C.	III	10.5 3 months, later 8.0	3,450 rads 1,848 rads	None	Marked regression	Alive with tumor 9 months	5 months after first treatment no tumor in bladder; bone metastases present

T.C. = transitional cell carcinoma.

der carcinoma patients following this method of combined therapy when only moderate tumor doses of radiation therapy are used. One would not expect similar results when either method of treatment is used alone with the same factors of treatment.

There was no increase in morbidity and mortality, nor was wound healing affected. The patients were able to tolerate the combined therapy satisfactorily, but close supervision must be maintained.

SUMMARY

The coordinated efforts of the urologist, radiation therapist, and chemotherapist, the more careful staging of the disease, improved techniques in surgery and anesthesia, and better antibiotics have all contributed to the better management of patients afflicted with bladder cancer.

The use of preoperative megavoltage radiation therapy is promising and data are presented to show that the end results may be improved following its use.

Experience with the use of 5-FU and preoperative radiation therapy has increased the percentage of tumor regression noted at the time of surgery over that anticipated when either agent is used alone.

It is important that continued experience be obtained with a large number of patients in order that a full evaluation of this combined regimen can be made. Whether or not there will be an improvement in the 5 year survival rates by using this method over other methods remains to be established.

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SEQUENTIAL CHEMOTHERAPY AND RADIATION THERAPY OF BUCCAL MUCOSA CARCINOMA IN SOUTH INDIA*

METHODS AND PRELIMINARY RESULTS

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BUCCAL mucosa cancer is a widespread disease in South India. It is characterized by wide regional invasion and low curability because of the usually advanced stage of the disease before the average patient appears for treatment (Fig. 1, *A* and *B*). The clinical features have been previously described.[13]

The accessibility of this tumor to direct measurement, tissue analysis, and photography makes it suitable for clinical trials with potentially favorable therapeutic modalities. Chemotherapy with methotrexate (MTX) followed by radiation therapy has been reported to increase survival of patients with epidermoid carcinoma as compared to patients treated with irradiation alone.[4] Similar studies with 5-fluorouracil (FU),[14] MTX,[10] and 5-iodo 2'-deoxyuridine (IUdR)[2] at the Yale-New Haven Medical Center have suggested possible benefits from combined chemotherapy and radiation therapy, but these have not been conclusive because of the small number of patients and the wide variety of tumor sites. It was decided to perform a clinical trial with radiation therapy alone (RAD) and with MTX, IUdR, and FU, each followed by irradiation in patients with advanced epidermoid carcinoma of the buccal mucosa. The initial route of drug administration was intravenous. It is planned to alter the route of administration to regional arterial infusion and to compare routes and dose schedules of the most effective drugs when significant differences between drugs are found.

CLINICAL MATERIAL

Patients with untreated epidermoid carcinoma arising in the gingival or buccal mucosa, Stage III or IV, were accepted for evaluation. The procedures of evaluation are shown in Table I. Conditions excluding the patient from the study included diseases such as tuberculosis, renal insufficiency or pregnancy that would render any of the possible treatments hazardous, and metastases below the clavicle. Severe anemia, hook-worm infestation, and infections were treated. Full dental extractions were generally performed. The hemoglobin level was adjusted to at least 10 gm. per cent, the white blood cell count was required to exceed 4,000 per cu. mm., and the blood urea to be less than 40 mg. per cent (serum creatinine clearance at least 35 liters per 24 hours). Careful caliper measurements of the primary tumors were made in three diameters since these tumors were accessible for volume estimation. Some tumors that were highly infiltrating with marked trismus, mandibular destruction, and extension into the hard palate could not be accurately measured, and in these situations the measurements were modified to include the one or two dimensions most easily palpated and the volume calculations

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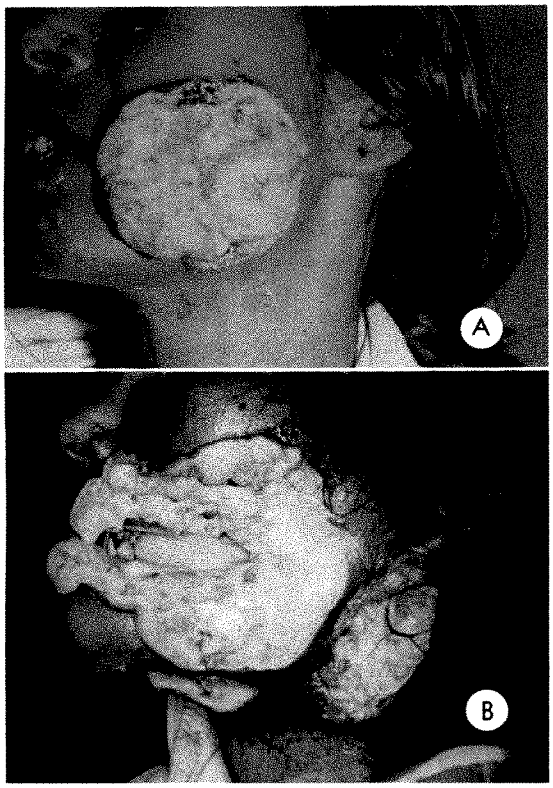


Fig. 1. (*A*) An example of the typically advanced state of disease upon presentation at the Christian Medical College Hospital. This patient had an epidermoid carcinoma of the buccal mucosa with perforation through the cheek, destruction of the mandible, but no palpable enlargement of the regional lymph nodes. (*B*) The same patient 127 days later. She refused treatment and left the hospital only to return with far advanced disease. There is massive destruction of the face and ulceration of regional lymph node masses. However, no low-lying cervical lymph nodes were palpated and the chest roentgenogram was negative.

were estimated. Trismus and the volumes of metastatic lymph nodes were also measured when present.

After having been found acceptable for the protocol, the patients were randomized into four groups by the method of Hill.[8] Random numbers were used in groups of 12 so that every sequence of 12 patients had an even distribution into the four treatment groups. No withdrawals were made beyond the point of randomization.

Table I

PROCEDURES OF EVALUATION

Laboratory Procedures
- Complete blood cell count
- Urinalysis
- Stool examination for ova and parasites ×2
- Biopsy
- Roentgenograms of mandible and chest
- Bone marrow smear
- Serum urea
- Serum creatinine clearance
- Plasma protein
- Serum folate ×2
- B_{12}
- Dietary consultation

Additional Procedures in Selected Cases
- Urinary FIGLU (formaminoglutamic acid) excretion following histidine loading
- Tissue histidase activity (normal and malignant tissue biopsy)
- Urine chromatography
- Serial serum folates

METHODS

The treatment protocols by group are shown in Table II.

RADIATION THERAPY

The prescribed dose for all patients was 6,500 rads delivered in a 6 week period using Co^{60} teletherapy with source skin distance of 80 cm. Those patients allocated to receive radiation therapy only were started immediately, while in cases allocated to receive chemotherapy followed by radia-

Table II

TREATMENT PROTOCOL

Treatment	Daily Drug Dose†		Radiation Dose
	mg./m²	~mg./kg.	
RAD	—	—	6,500 rads in 6 weeks
MTX-RAD*	7	0.2	
IUdR-RAD*	2,840	90	
FU-RAD*	520	15	

RAD = Radiation Therapy; MTX = Methotrexate; IUdR = Iododeoxyuridine; FU = Fluorouracil. (These abbreviations apply to Tables II–IX).

* Radiation therapy began on Day 10–15.

† 5 consecutive intravenous injections.

tion therapy, the radiation therapy was begun between Day 10 and Day 15 following the initiation of the chemotherapy. However, in all cases the level of mucositis was observed and treatment was delayed until it subsided below the second degree level. Radiation therapy was generally delivered by means of right angled wedge-filtered fields directed from anteriorly and laterally and planned to encompass all visible and palpable disease with generous margins superiorly and inferiorly. In extensive disease approaching the midline, cross-firing or other angles were planned. The dose to the cervical spinal cord was limited to less than 4,500 rads. In cases where a severe third degree mucositis developed during the prescribed treatment, interruption of therapy was carried out for one week or less and the total dose was, in these cases, raised to 7,000 or 7,500 rads. The usual average daily tumor dose, calculated at the minimal percentage contribution within the tumor volume on the contour, was 217 rads given through one field daily, 5 days a week.

DRUG THERAPY

The dosage was derived from experience at Yale-New Haven Medical Center. In all cases the injections were given intravenously over a period of a few minutes to a few hours as in the case of IUdR. It was found that IUdR was more toxic in the Indian patients than in the group at Yale and the dosage was reduced. Conversion of dosage in milligrams per kilogram to milligrams per square meter was performed because of the diminutive stature and weight of many of the Indian patients and in accordance with recommended practice.[11] The full prescribed dose of drug was given over 5 consecutive days but in some instances interruption or elimination of the final dose was made because of undue toxic reactions.

Measurements of response and reactions. Serial recordings at least twice weekly were performed on all patients under active treatment and consisted of the following:

1. Peripheral leukocyte counts.
2. Oral mucositis—first degree mucositis was scored when erythema occurred, second degree when discrete to semiconfluent patches of whitish membrane developed, and third degree when confluent patches of whitish membrane were noted.
3. Enteritis—first degree enteritis was noted when there were 2 to 5 loose bowel movements daily or vomiting, second degree at greater than 5 loose watery movements, and third degree with severe diarrhea with mucus or blood and marked dehydration.
4. Tumor effect—tumor volume was measured serially by caliper, generally by one examiner throughout the course of treatment to insure maximum consistency.[1,5] Photography and, in some cases, serial biopsies were also done.

All reactions and responses were recorded on a specially designed graph similar to one developed by Friedman and Daly.[4] Follow-up examinations were also recorded on this form.

SURGERY

Patients were evaluated for surgery 6 weeks following completion of radiation therapy. Those cases with apparent residual or recurrent disease were selected for resection, generally hemimandibulectomy and local soft tissue resection.

RESULTS

One hundred patients have been admitted to the study in the first 13 months of the program. The distribution of sex, age, tumor volume, bone involvement, and T-N classification are shown in Tables III and IV by treatment groups. Analysis of the listed characteristics shows a lower male to female ratio, a lesser mean tumor volume, and a lower percentage of bone involvement in the radiation only group as compared to the other three groups. In the comparison of T-N distribution, the group

Table III

COMPARISON OF TREATMENT GROUPS

Group	Sex		Mean Age (yr.)	Mean Tumor Volume (cm.^{3})	Bone Involvement	
	M	F			+	−
RAD	10	15	51.6±2.1* (27–73)† 10.6‡	46.0±10.6* (3–240)† 51.0‡	14 (56%)	11
MTX-RAD	13	12	49.1±1.9 (30–74) 9.7	83.4±12.9 (19–310) 63.4	18 (75%)	6
IUdR-RAD	14	9	48.0±2.1 (28–65) 10.2	92.0±25.5 (6–530) 116.9	14 (70%)	6
FU-RAD	13	12	48.8±1.8 (30–69) 9.2	83.8±19.0 (4–400) 95.0	16 (64%)	9
Total	50	48			62	32
			Chi-square = 2.11 (D.F. = 3) P≈0.5		Chi-square = 2.20 (D.F. = 3) P≈0.5	

* Mean and standard error.
† Range.
‡ Standard deviation.

Table IV

T-N DISTRIBUTION IN TREATMENT GROUPS

Group	T_3	T_4	N_0	N_1	N_2	N_3
RAD	4 (17%)	20 (83%)	1 (4%)	5 (21%)	4 (17%)	14 (58%)
MTX-RAD	1 (4%)	24 (96%)	3 (12%)	0 (0%)	4 (16%)	18 (72%)
IUdR-RAD	2 (9%)	19 (91%)	2 (10%)	3 (14%)	1 (5%)	15 (71%)
FU-RAD	10 (40%)	15 (60%)	4 (17%)	5 (21%)	3 (12%)	12 (50%)
Total	17 (18%)	78 (82%)	10 (10%)	13 (14%)	12 (13%)	59 (63%)
	Chi-square = 12.58 (D.F. = 3) P≈.01		Chi-square = 9.94 (D.F. = 9) P≈0.5			

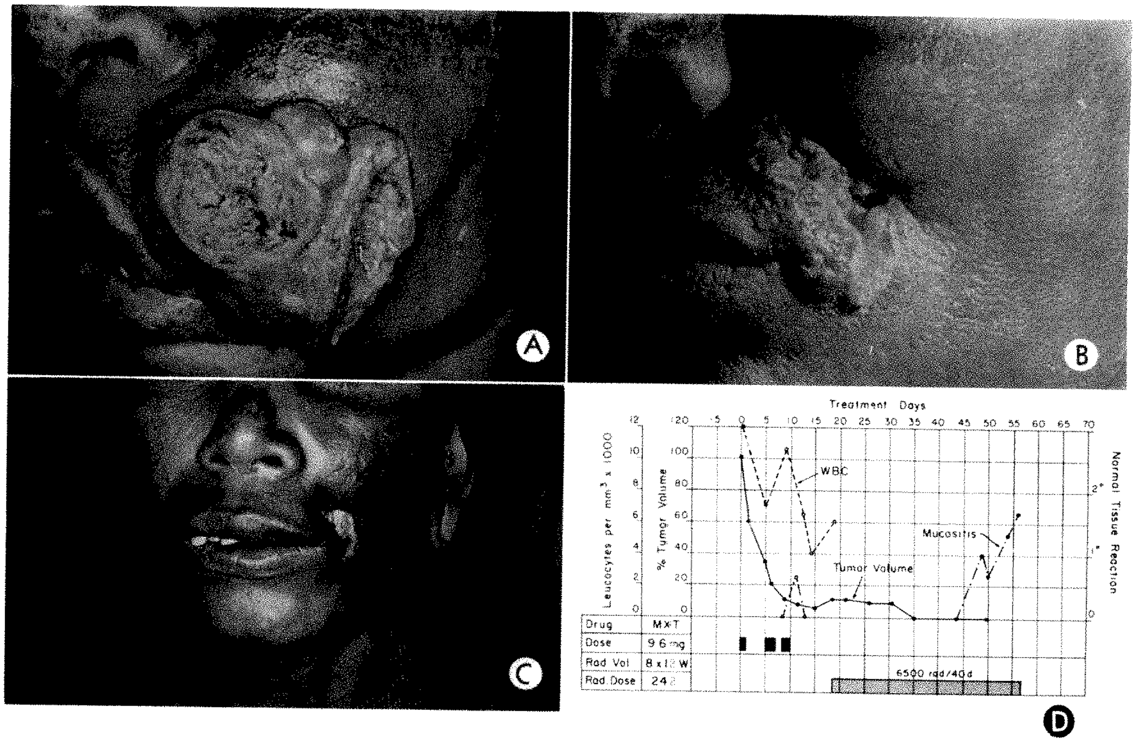


FIG. 2. (*A*) Day 0. This patient has a lesion involving the left buccal mucosa with invasion of the maxilla. There is surrounding edema. (*B*) Day 15. The tumor has regressed considerably at this time, 5 days following completion of a course of systemic methotrexate (MTX). (*C*) Day 60. There is no gross tumor by completion of a course of radical radiation therapy. A residual orocutaneous fistula marks the area of original perforating tumor. (*D*) Graphic representation of the treatments and the normal malignant tissue reactions of this patient.

receiving 5-fluorouracil and radiation therapy had a significantly larger percentage of patients with T_3 lesions than was noted in the other three groups. These characteristics were not included in the randomization process and it is expected that the discrepancies of possible prognostic factors will diminish as the study continues. It was possible to evaluate short term effects of treatment in 87 patients with follow-up periods of 2 to 14 months. Three examples are shown in Figures 2, *A–D*; 3, *A–D*; and 4, *A–D*.

TUMOR VOLUME CHANGES

The immediate changes of tumor volume following chemotherapy are shown in Figure 5. All three drugs produced a prompt volume reduction in a large percentage of patients. These effects can be

→

FIG. 4. (*A*) Day 0. A patient with an extensive carcinoma involving the left cheek with mandible erosion and a large fixed upper cervical lymph node. (*B*) Day 9. Result of systemic iododeoxyuridine (IUdR). The tumor regressed considerably and the cervical lymph node became markedly fluctuant. At this time radical radiation therapy was initiated. (*C*) Day 75. The result of incomplete radiation therapy. The patient absconded midway through the schedule course of radiation therapy, then returned to receive a further incompleted course. However, a total regression of disease was noted at this point. Local recurrence in bone developed 5 months later. (*D*) Graphic representation of the events described above.

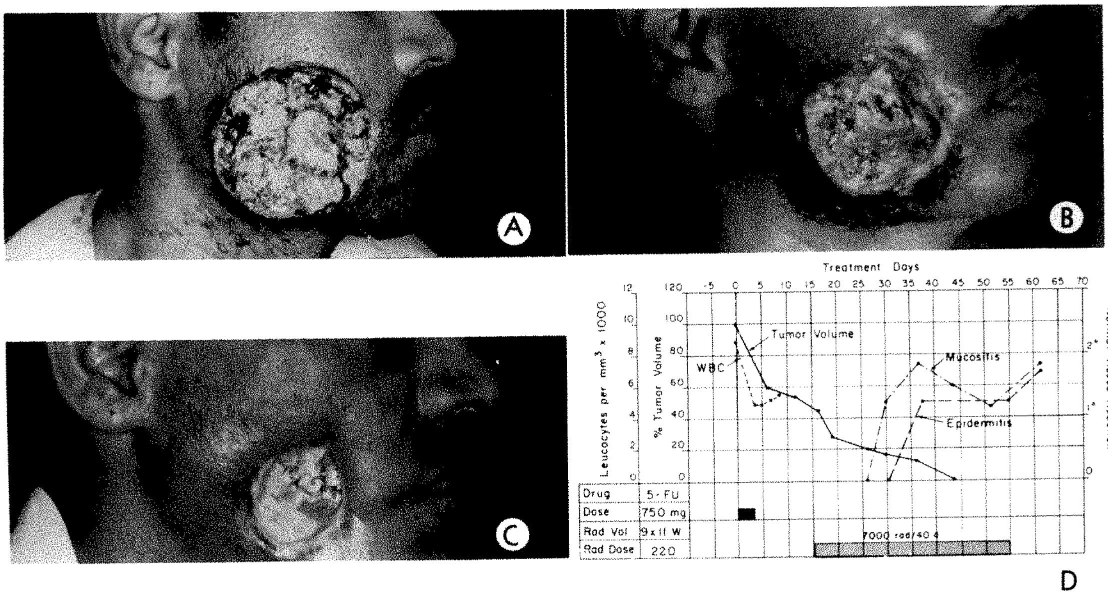
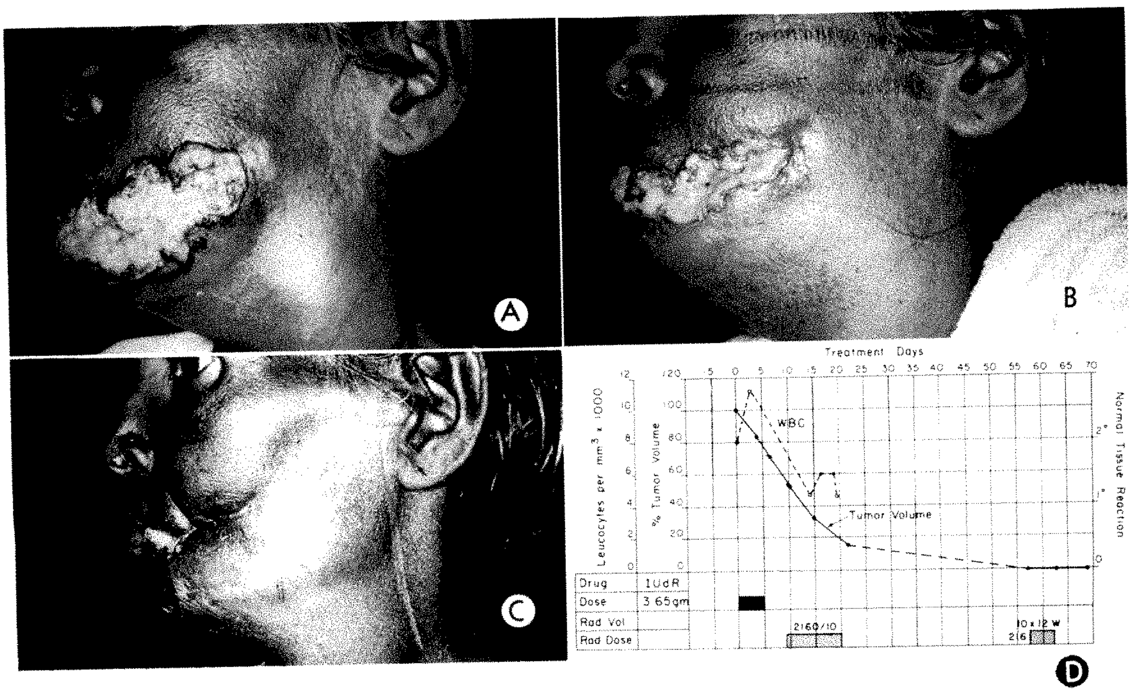


Fig. 3. (*A*) Day 0. There is an ulcerating tumor involving most of the right cheek and producing marked trismus, an orocutaneous fistula, and erosion of the mandible. (*B*) Day 10. The exophytic portion of the tumor has regressed considerably following a course of systemic fluorouracil (FU). (*C*) Day 93. Result following completion of radical radiation therapy. Local control persisted but a marginal recurrence in the zygomatic region was noted 6 months later. In retrospect, the dimensions of the radiation field were established on the basis of the apparent tumor volume *following* instead of *preceding* chemotherapy. It appears from this and other cases that tumor margins are not sufficiently sterilized by preliminary chemotherapy to warrant any reduction of initial radiation volumes. (*D*) Graphic representation of the treatments and the normal and malignant tissue reactions of this patient.



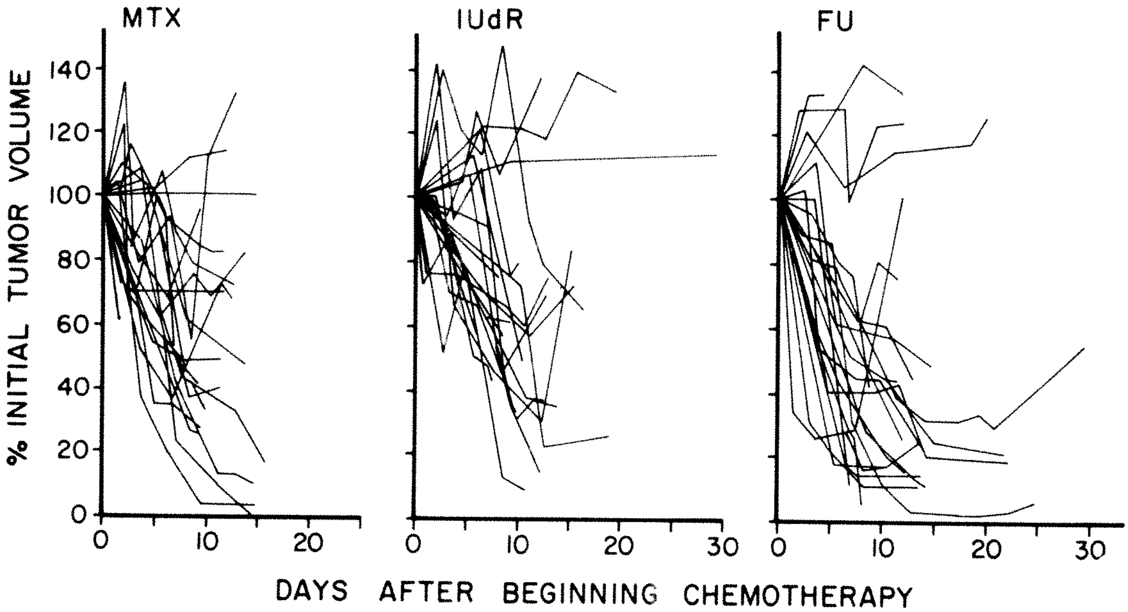


Fig. 5. Composite graphs of tumor volume curves during and following chemotherapy. All tumor volumes were normalized to 100 per cent on Day 0, the day of initiation of treatment. All 3 drugs produced a large percentage of significant tumor regressions. The curves end at the time of initiation of radiation therapy.

evaluated up to the time of initiation of radiation therapy. The relationships of the serum folate levels to tumor regression following drug therapy are shown in Table V. Folate deficient patients showed a greater tumor regression pattern with a 10 per cent level of significance. The number of responses to individual drugs are too few to evaluate.

Tumor volume changes following radiation therapy are shown in Figure 6. The rate of regression for radiation therapy alone was generally less than that for the drug responses. MTX and FU appeared to produce more prompt regression both alone and in combination with radiation therapy.

TOXICITY

The drugs produced toxicity of a degree varying from no detectable reaction to

Table V

Relation of Serum Folate Levels to Tumor Response Following Chemotherapy

Group	No.	Serum Folate Levels			
		<5 mμg./ml.		5 or more mμg./ml.	
		Responses	Non-Responses	Responses	Non-Responses
MTX	20	7	5	4	4
IUdR	21	5	3	4	9
FU	24	10	2	7	5
Total	65	22 (34%)	10 (15%)	15 (23%)	18 (28%)

Chi-square = 2.90
(D.F. = 1)
0.10 > P > 0.05
Response = 50% or more tumor volume reduction.

death. These findings are shown in Table VI and appear unrelated to the serum folate level. Toxicity, however, appears related to tumor response as shown in Table VII. Radiation therapy also produced reactions ranging from none detectable to one death which resulted from severe dehydration during treatment leading to renal failure. In all the treatment groups it was not possible to note a significant difference in reactions but there was a suggestion that FU produced a larger percentage of toxic reactions as well as a larger percentage of tumor responses to drug alone but not to subsequent radiation therapy. All these data are summarized in Table VIII.

DEGREE OF TUMOR CONTROL

The follow-up period for this initial group of patients extends from 2 to 14 months. An estimate only of possible tumor curability is possible (Table IX). These findings are analyzed both for the group entering the protocol and those completing the protocol. The difference in patient number between these two groups consists of 4 deaths during treatment and a large number of "absconders" (patients who leave during treatment to return to their homes). The problem this raises is particularly difficult in the follow-up period since evaluation for surgery is scheduled at 6 weeks post completion. A large percentage

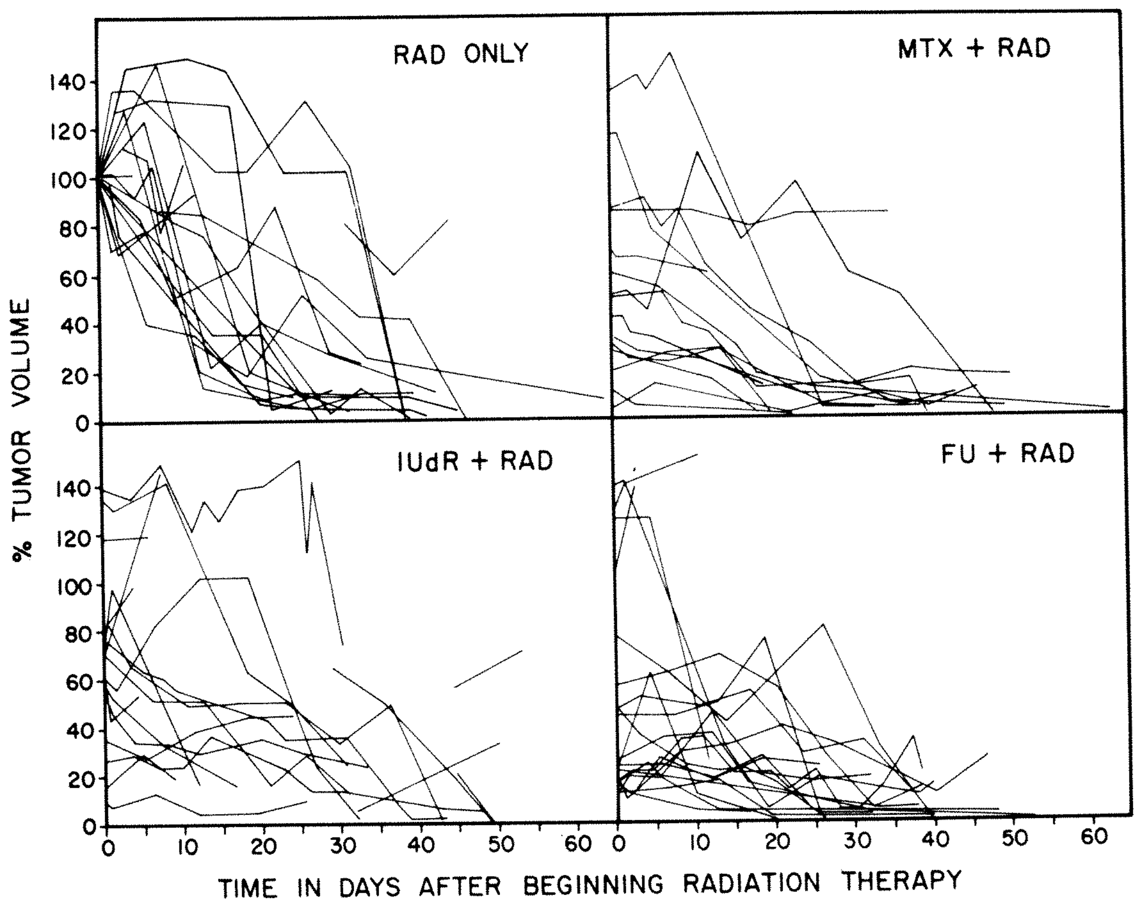


Fig. 6. Composite graphs of tumor volume curves during and following radiation therapy. The same scale of normalized volumes as in Figure 5 is used. In the 3 groups receiving preliminary chemotherapy the tumor volumes at the time of radiation therapy are significantly reduced. The subsequent regressions appeared accelerated in these same groups.

Table VI

RELATION OF SERUM FOLATE TO DRUG TOXICITY

Group	Total	Serum Folate							
		<5 mμg./ml.				5 or more mμg./ml.			
		+++	++	+	o	+++	++	+	o
MXT	20		1	3	5	1	2	1	7
IUdR	21		1	2	5	1		2	10
FU	24	1	4	2	5		1	6	5

Chi-square = 0.5111
(D.F. = 1)
$0.50 > P > 0.30$

Drug Toxicity
+++ = Death.
++ = 3° enteritis or mucositis and/or white blood cell count of <2,000.
+ = 2° enteritis or mucositis and/or white blood cell count of 3,000 to 2,000.
o = Less than above.

Table VII

RELATION OF TUMOR RESPONSE TO DRUG TOXICITY

Group	No.*	Responders		Non-Responders	
		Reaction	No Reaction	Reaction	No Reaction
MTX	19	6	5	1	7
IUdR	20	3	6	2	9
FU	23	9	7	4	3
Total	62	18	18	7	19

Chi-square = 3.37
(D.F. = 1)
$0.05 > P > 0.02$

* 3 deaths related to drug toxicity not included.

Table VIII

TUMOR RESPONSE AND TOXICITY FOLLOWING CHEMOTHERAPY AND RADIATION THERAPY

Group	Treatment	No.	Drug Effect				Radiation Effects				
			Tumor Responses*		Toxicity		No. Completing Radiation Therapy	Tumor Responses†		Toxicity	
			No.	Per Cent	No. Deaths	Other Reactions‡		No.	Per Cent	No. Deaths	Other Reactions‡
I	RAD	22	—	—	—		15	8	53	1	13
II	MTX-RAD	20	11	53	1	7	17	14	82	0	13
III	IUdR-RAD	21	9	43	1	5	16	10	62	0	11
IV	FU-RAD	24	17	71	1	13	18	12	67	0	15
Total		87	37	57§	3	25	66	44	67	1	52

* Drug tumor response = 50% or greater volume reduction.
† Radiation tumor response = 90% volume reduction at any time following completion of radiation therapy.
‡ Other reactions = 2° to 3° mucositis or enteritis and/or white blood cell count of 3,000.
§ Per cent calculated from chemotherapy group only.

Table IX

APPARENT TUMOR CONTROL IN PATIENTS FOLLOWED 2–14 MONTHS

Group	No.	Individuals Completing Protocol		Individuals Tumor Free				
		No.	Per Cent	No Surgery	With Surgery	Total	Per Cent of Patients Entering Protocol	Per Cent of Patients Completing Protocol
RAD	22	15	68	3	2	5	23	33
MTX-RAD	20	16	80	—	3	3	15	19
IUdR-RAD	21	16	76	2	1	3	14	19
FU-RAD	24	18	75	3	3	6	25	33
Total	87	65	75	8	9	17	19	26

of patients failed to appear at this time only to return later with gross recurrent unresectable disease.

DISCUSSION

Chemotherapy with systemic methotrexate, iododeoxyuridine, or fluorouracil, produced striking tumor regressions in a large percentage of this group of South Indian patients with untreated buccal mucosa carcinoma. These regressions can be favorably compared to those reported with intra-arterial infusion.[7,9] The technical problems of intra-arterial infusion chemotherapy[12] may possibly detract from the theoretic advantages of delivering a cancericidal drug directly into the arterial supply to a regionally localized tumor. However, these approaches should be compared in a planned study. A correlation with low serum folate levels and drug response of tumors was noted, although host toxicity could not be correlated with low folate levels. The high percentage of oral cancer patients with deficient serum folates has also been previously noted.[6] The subsequent responses to radiation therapy appeared to be greater in the drug treated group than in the control radiation therapy group. Detailed clinical observations are necessary in order to determine possible enhancement of tumor response[3] as well as normal tissue reactions. The short-term apparent tumor control, however, was found to be similar in all four treatment groups. The failure to control disease in the majority of patients was due to local recurrence of disease, particularly in the vicinity of involved bone. It is therefore likely that in this therapeutic approach, cancer cells cannot be sterilized in the center of these massive lesions with bone invasion. The fact that 9 out of 12 surgical resections in the entire group have resulted in apparent success indicates that surgery should be routinely employed in all patients with demonstrated bone destruction. It must be emphasized that all the cases admitted to this study were considered originally to have unresectable lesions. More patients had resection in the radiation therapy group than in any of the three other groups because of a larger number with known uncontrolled disease; paradoxically, in the drug treated groups, the rate of early complete regression was greater and fewer cases were selected for surgery. It is, therefore, not possible yet to determine if a significant therapeutic advantage does or does not exist in one or more of the treatment groups. This study will continue until this question can be answered.

CONCLUSION

Patients with advanced buccal mucosa carcinoma have been treated in a four group clinical trial consisting of Co^{60} tele-

therapy alone, methotrexate (MTX) followed by radiation therapy, iododeoxyuridine (IUdR) followed by radiation therapy, and fluorouracil (FU) followed by radiation therapy. Eighty-seven patients were evaluated for short-term results.

All three drugs produced marked tumor regressions in an average of 57 per cent of the cases. Radiation therapy alone produced essentially total regression in 8/15 (53 per cent); and, when combined sequentially with methotrexate, in 14/17 (82 per cent); with iododeoxyuridine, in 10/16 (62 per cent); and with fluorouracil in 12/18 (67 per cent). Despite these regressions, the majority of lesions recurred and only 19 per cent apparent salvage has been achieved, most of these patients having been subsequently subjected to resection of the lesion.

Preliminary drug therapy appears to enhance tumor regression following radiation therapy but no significant difference is yet noted in freedom from tumor recurrence, presumably because of highly resistant residual neoplasm in bone. Routine resection of diseased bone is now planned. The study will continue.

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CLINICAL EVALUATION OF COMBINED RADIATION AND CHEMOTHERAPY IN GASTROINTESTINAL MALIGNANCIES*

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THE fluorinated pyrimidine compounds, especially 5-fluorouracil, have definite effectiveness as antineoplastic agents in human malignant tumors. It has been especially observed that patients with cancer of the gastrointestinal tract have responded to these drugs. In the past few years Foye *et al.*,[7] Allaire *et al.*,[1] and Frank *et al.*[9] have published data concerning a potentiation effect of radiation when 5-fluorouracil was added to radiation therapy.

This preliminary report presents our clinical experience with 61 patients with advanced carcinoma of the gastrointestinal tract, who were studied over the same time period and were treated by: (a) 5-fluorouracil alone; (b) 5-fluorouracil in combination with radiation therapy; and (c) radiation therapy alone.

The purpose of our investigation was: (1) to show in a short study the effectiveness, or lack of it, of these three different methods in the treatment of gastrointestinal malignancy; and (2) to determine the best method for symptomatic treatment of patients with advanced cancer of the gastrointestinal tract.

MATERIALS AND METHODS

All patients included in this study had proved malignancy by pathologic examination of a biopsy specimen. They all were in a stage of the disease when in addition to the primary site, metastatic lesions were present either in mesenteric lymph nodes, liver or bones.

When radiation therapy was given alone, the dose ranged between 3,000–7,000 r in 20–30 days and was adjusted in most cases to the patient's tolerance. When radiation therapy was given in combination with intravenous injections of 5-fluorouracil, the amount of radiation given was in the same range as when given alone, but the duration of therapy was longer (average 45 days). When used alone, without radiation therapy, 5-fluorouracil was administered intravenously in doses of 15 mg./kg. on day 1, 2, 3, and 4; 500 mg. was then administered intravenously biweekly until toxicity developed.

When 5-fluorouracil was given in combination with radiation therapy, the dose of 500 mg. biweekly was administered intravenously during the whole course of radiation therapy, provided that no toxicity (bone marrow, gastrointestinal) appeared during that period of time. If the bone marrow showed signs of depression (white blood cell count below 3,000 cells/mm.^{3}; platelets below 100,000 cells/mm.^{3}) the drug was stopped until the values of white blood cells and platelets returned to normal.

By accepting the fact that a time/dose relationship exists in radiation biology, the total dose (in r) was first divided by time to obtain a "daily" r value, which could be used as a single figure to compare statistically with "response." A simple method of scoring response or treatment efficiency was decided upon. This gave a value of 0 to those cases which failed to respond (no change or worse); a value of 1 to subjective improvement; and a figure of 2 for an objective response. When subjec-

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tive and objective responses were present together a value of 3 was assigned. The reason that no minus values were used was the difficulty encountered in trying to decide whether patients became worse because of their disease or because of the treatment itself.

By means of these two values (x = therapy in r/day; y = response) a correlation study was then carried out by standard methods. This was designed to answer whether or not a direct correlation exists between the dose/day of ionizing radiation delivered within the patient's tolerance, and the ultimate clinical response. As shown in Table I this study provides an r value of 0.332; $SE_r = 0.288$; $p = 0.135$. There is thus a positive correlation, but only to a low degree, which proves in this series insignificant.

In Table II the analysis of the data measuring the Strandqvist value percentile divided by 100 rather than the r/day figure for radiation therapy, against the same scoring of clinical response revealed the following values: $r = 0.551$; $SE_r = 0.29$; and $p = 0.03$.

There is, thus, by using these new figures, a positive correlation between the amount of radiation measured as a ratio of ideal Strandqvist values and the response of gastrointestinal malignancy. The significance of this novel approach to radiation measurement will be discussed later.

Using in Table III the assumption that the amount of cytotoxic drug given over a period of time possesses a dose/time relationship and assuming that this is a direct relationship in terms of response of a sensitive tumor, a single figure for radiation therapy was obtained by dividing the dose (in gm.) by the time (in days). By assignment of the same values (0, 1, 2, 3) for therapeutic responses, a correlation study of the tabular values revealed the following: $r = 0.73$; $SE_r = 0.35$; $p = 0.018$.

There is, therefore, a positive correlation of drug and response with cancer of the colon, when that response is measured against the amount of drug that can be delivered in a specific period of time.

Tables IV and V demonstrate results of a very small number of patients with carcinoma of the stomach and rectum treated

Table I

IONIZING RADIATION ALONE

Patient	Radiation Dose (r/days)	Response*	Site of Tumor
1	7,000/34	NC	Rectum
2	3,900/17	W	Colon
3	4,100/29	S and O	Colon
4	7,000/31	S	Rectosigmoid
5	3,300/15	S	Colon
6	4,500/27	S	Rectum
7	7,100/30	S	Rectum
8	900/8	NC	Transverse colon
9	5,700/18	S and O	Stomach
10	5,300/18	S	Rectum
11	5,000/37	W	Colon
12	3,200/4	S and O	Rectum
13	5,700/27	S and O	Rectum
14	7,750/43	S and O	Rectum

* NC—no change; W—worse; S—subjective improvement; O—objective improvement.
Statistics: $r = 0.332$; $SE_r = 0.288$; $p = 0.135$.

Table II

IONIZING RADIATION ALONE

Patient	Radiation as Strandqvist Percentile	Response*	Site of Tumor
1	121	NC	Rectum
2	83	NI	Colon
3	76	S and O	Colon
4	128	S	Rectosigmoid
5	73	S	Colon
6	79	S	Rectum
7	129	S	Rectum
8	24	NC	Transverse colon
9	119	S and O	Stomach
10	110	S	Rectum
11	86	NI	Colon
12	100	S and O	Rectum
13	107	S and O	Rectum
14	127	S and O	Rectum

* NC—no change; NI—no improvement; S—subjective improvement; O—objective improvement.
Statistics: $r = 0.551$; $SE_r = 0.29$; $p = 0.03$.

TREATMENT OF UNRESECTABLE ADENOCARCINOMAS OF THE STOMACH WITH A COMBINATION OF 5-FLUOROURACIL AND RADIATION*

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COMBINED chemotherapy and irradiation in the management of malignant disease is a subject of current interest. Radiation therapy is essentially a local agent that is capable of producing partial or complete regression in a large number of malignant tumors. Systemic chemotherapy may produce regressions in patients with wide-spread malignant disease, but it is often accompanied by a high degree of toxicity. Studies[6] of mice with mammary carcinoma have indicated that a combination treatment with 5-fluorouracil* (5-FU) and irradiation resulted in increased inhibition of tumor growth as well as in prolonged survival when compared to either mode of therapy alone. Data from a controlled study[1,4] of bronchogenic carcinoma in man were suggestive of an increase in survival time after therapy with irradiation and 5-FU. von Essen and co-workers[7] reported a study, using a method of interior controls, in which radiation and 5-FU were employed in the treatment of various tumors. This study did not demonstrate a significant alteration in tumor response by the addition of 5-FU to x-irradiation.

Since 5-FU has shown its most unique clinical usefulness in the treatment of gastrointestinal carcinomas, it is hoped that this class of neoplasm will be a more fertile proving ground for the effectiveness of combined therapy. A large number of such studies, with varied and conflicting opinions, have appeared in the literature. None of these studies, however, have had adequate controls.

Unresectable tumors of the stomach represent a problem for the cancer therapist and radiation therapy has not had a major part in the management. Therapy with the fluorinated pyrimidines, however, has been shown to be capable of inducing a regression in some patients with gastric adenocarcinomas. We undertook a pilot study[5] to determine (1) the dosage of 5-FU that would be relatively safe and tolerable in combination with supervoltage radiation therapy, and (2) whether 5-FU combined with supervoltage radiation therapy was capable of producing useful palliation in a sufficient number of patients to justify further systematic evaluation. Results of this study showed that a total dose of 40 to 50 mg./kg. of body weight of 5-FU given in 3 to 4 divided doses by rapid intravenous injection at the onset of a course of supervoltage radiation therapy was relatively safe and tolerable. Larger doses were accompanied by excessive toxicity and mortality.

Because a sufficient number of patients in the pilot study achieved objective and subjective palliation, we conducted a controlled study[3] of the use of radiation alone and radiation plus 5-FU in unresectable gastrointestinal neoplasms. From the study,[3] it was concluded that in gastric

* The 5-fluorouracil for this study was supplied by Hoffman-La Roche, Inc.

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From the Mayo Clinic and Mayo Foundation: Sections of Oncology (Drs. Childs, Holbrook, and Colby, Therapeutic Radiology; Drs. Reitemeier and Moertel, Medicine).

adenocarcinomas the survival rate of patients who received the combination treatment was sufficiently greater than that of the patients who received radiation alone to justify increasing the number of patients in the series.

The present series includes the 15 patients reported in the previous study[3] and 27 additional patients treated under the same protocol.

MATERIALS AND METHODS

To be eligible for the study, a patient had to have histologically proved unresectable adenocarcinoma of the stomach, which at operation or on clinical examination was found to be localized and without evidence of distant metastases. All known disease had to be localized to a region that could be encompassed by a radiation field of not more than 20 by 20 cm.

Each patient in the series was given supervoltage radiation therapy delivered by either a cobalt 60 teletherapy unit or a 6.3 million volt linear accelerator. Radiation therapy was administered 6 days each week at a rate of 900 to 1,200 rads per week, to a total tumor dose of between 3,500 and 4,000 rads. In addition to the radiation, each patient was to receive either 5-FU or saline, the selection being made on a random basis. Neither the patients nor the investigators were aware of this assignment. The daily dose of 5-FU for each patient was 15 mg./kg. of actual or ideal body weight, whichever was less. It was administered by the rapid intravenous technique on consecutive treatment days, starting with the first day of radiation therapy, until a total dose of from 40 to 50 mg./kg. had been reached. When the treatment code called for placebo, an equivalent volume of isotonic saline was administered. Each patient was observed for evidence of toxicity during the course of the irradiation, and the status of each was re-evaluated at intervals of 3 months, until either the disease progressed or death intervened.

Table I

COMPOSITION OF GROUPS WITH UNRESECTABLE GASTRIC ADENOCARCINOMA TREATED BY RADIATION AND SALINE OR 5-FU

	Saline	5-FU
No. of Patients	22	20
Age (yr.): Mean	55.6	57.7
Range	33–70	40–71
Sex: Male	16	15
Female	6	5
Dukes' Classification B	2	2
C	17	18
Histologic Grade: 1 and 2	3	1
3 and 4	19	19
Proof of Extent: Surgical	19	18
Clinical	3	2
Primary Tumor	16	12
Recurrent Tumor	6	8

RESULTS

When the treatment code was broken, the composition of the two groups was of that shown in Table 1. There does not seem to be any identifiable bias between the groups.

Toxicity. Nausea and vomiting occurred in 71 per cent of the group receiving 5-FU and in 77 per cent of those receiving saline. Nausea and vomiting when present in either group were not severe and did not result in major difficulty in administering treatment. The leukocyte count decreased below 4,000/cu. mm. in 86 per cent of the patients receiving 5-FU and below 2,000 in 43 per cent. In the group receiving saline, 27 per cent of the patients had leukocyte counts below 4,000 while none had counts below 2,000. Significant thrombocytopenia did not occur. Stomatitis and diarrhea occurred only infrequently, and when they did occur, they were minor. There were no deaths as a result of treatment.

Survival. The survival curves for the two groups of patients are shown in Figure 1.* Analysis of these curves indicates that the differences are significant at the $P<.05$

* The method of calculating the survival rates is described in Reference 2.

level but not at the P <.01 level. Therefore, this study is highly suggestive of more favorable survival in the combined therapy group, although there was no firm evidence of this. Continued study seems to be indicated.

At the present time, the mean survival in the placebo group is 5.7 months, with 1 patient alive at 10 months. The mean survival in the combined therapy group is 11.6 months, with 3 patients alive at 16, 24, and 46 months, respectively.

We would like to emphasize that these results apply only to the type and extent of disease studied, to the dosage of radiation used, and to dosage schedule of 5-FU employed.

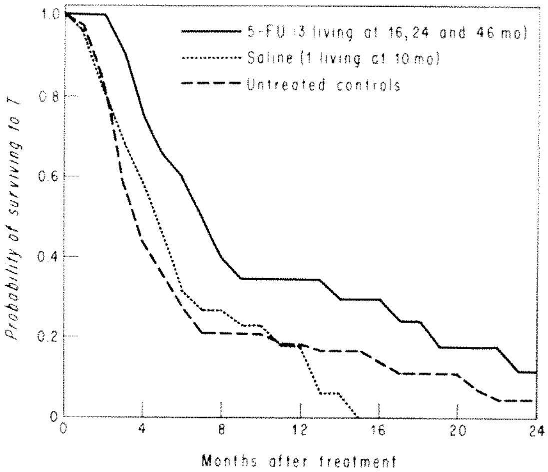

Fig. 2. Survival curves in unresected gastric adenocarcinoma. Groups treated with radiation and saline or 5-FU and group without treatment.

DISCUSSION

This study was designed to compare the clinical results of treatment with radiation alone with those of combined 5-FU and radiation. We did not study concurrently similar patients not treated or patients treated with 5-FU alone. In the former situation we have attempted to estimate survival by studying a comparable group of patients with unresectable gastric adenocarcinoma seen at the Mayo Clinic between 1955 and 1958. The patients were chosen on the basis of the operative findings (unresectable, no distant metastases, complete coverage with a 20×20 cm. field). After the selection, survival data on these patients were gathered. The resulting survival curve and the survival curves of the two groups in the present study are shown in Figure 2. Although this evaluation represents an attempt to choose a group of patients similar to those in the present study, it is a retrospective study and therefore its validity is subject to question. It would seem reasonable to suggest, however, that radiation therapy in the dose used in this study does not appreciably affect survival of patients with unresectable gastric carcinoma.

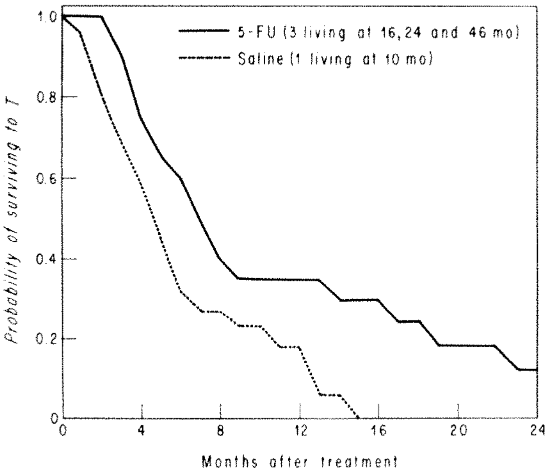

Fig. 1. Survival curves in unresected gastric adenocarcinoma. Groups treated with radiation and saline or 5-FU.

CONCLUSION

Since a statistical analysis of the survival curves of the two treatment groups is suggestive of a real difference, we intend to extend this study to include a larger group of patients.

Should the combination of 5-FU and radiation prove to be of established value in unresectable gastric adenocarcinoma, consideration should be given to a clinical trial of this combination treatment as an adjuvant to surgery in patients with

resectable gastric adenocarcinoma and poor prognosis.

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Table III

CARCINOMA OF COLON TREATED WITH 5-FLUOROURACIL ALONE

Patient	Dose of Drug (gm./days)	Results*
1	23.0/23	S and O
2	20.0/45	S and O
3	4.35/5	S
4	20.0/40	S and O
5	6.45/12	S and O
6	15.0/98	S and O
7	12.36/60	NI
8	6.10/67	NI
9	5.0/7	NI
10	4.5/18	S and O

* S—subjective improvement; O—objective improvement; NI—no improvement.
Statistics: $r=0.73$; $SE_r=0.35$; $p=0.018$.

with 5-fluorouracil alone. No statistical conclusions are warranted; however, it may be noted that 3 of the 4 patients with stomach lesions, but only 1 of the 4 patients with rectal lesions, demonstrated objective benefit.

In combination therapy of carcinomas of the large bowel as shown in Table VI, the radiation Strandqvist value was again divided by 100, while values of 0, 1, 2 and 3 were assigned as before to responses. In the combined study the drug value was simply added to the value of the divided Strandqvist percentile and a correlation study carried out on a combined therapy index

Table IV

CARCINOMA OF STOMACH TREATED WITH 5-FLUOROURACIL ALONE

Patient	Dose of Drug (gm./days)	Results*
1	4.2/10	S and O
2	3.5/4	NI
3	5.75/13	O
4	5.0/10	S and O

* S—subjective improvement; O—objective improvement; NI—no improvement.
Because of the small number of patients no correlation study is warranted. It is, however, interesting that 3 of the 4 patients had an objective response while 1 showed no improvement.

Table V

CARCINOMA OF RECTUM TREATED WITH 5-FLUOROURACIL ALONE

Patient	Dose of Drug (gm./days)	Results*
1	4.80/16	S and O
2	14.0/14	NI
3	3.30/5	NI
4	2.50/5	S

* S—subjective improvement; O—objective improvement; NI—no improvement.
Again because of the extremely small number of patients, no correlation study was attempted and it may be seen that only 1 of 4 patients had an objective response, 2 did not respond while 1 subjectively felt better.

against response. The values obtained were $r=0.530$; $SE_r=0.29$; $p=0.03$. Positive correlation does exist with a p value which is significant.

A Therapy Index was calculated (Table VII) by the simple addition of the radiation value and the drug dosage, and correlation was looked for between treatment and response in carcinoma of the stomach treated by a combination of drug and radiation. In view of the small number of pa-

Table VI

CARCINOMA OF THE LARGE BOWEL TREATED WITH DRUG AND RADIATION THERAPY

Patient	Dose of Drug (gm./days)	Radiation as Strandqvist Percentile	Results*
1	0.85/18	91	S and O
2	7.3/92	66	O
3	0.5/1	31	S
4	25/75	100	O
5	6/30	65	S and O
6	4.85/36	48	NI
7	3.5/11	83	NI
8	6.6/105	54	NI
9	2.0/9	98	NI
10	20.2/180	80	S and O
11	10.5/16	78	NI
12	3.75/5	82	S and O
13	7.5/18	48	NI
14	13.95/180	98	S and O

* S—subjective improvement; O—objective improvement; NI—no improvement.
Statistics: $r=0.530$; $SE_r=0.29$; $p=0.03$.

TABLE VII

CARCINOMA OF STOMACH TREATED WITH COMBINED THERAPY

Patient	Dose of Drug (gm./days)	Radiation as Strandqvist Percentile	Results*
1	7.4/20	54	NI
2	2.7/12	97	O
3	3.845/51	83	S and O
4	6.20/31	96	S and O
5	4.0/35	88	S and O
6	3.0/30	95	S and O
7	4.2/35	94	S and O
8	3.23/14	40	NI

* S—subjective improvement; O—objective improvement; NI—no improvement.

tients, it is merely concluded that 6 patients showed objective response of tumor to treatment, while 2 of the 8 failed to respond. In addition, 5 of the 8 patients experienced subjective palliation of pain.

Table VIII records the results of combination therapy in 7 patients with carcinoma of the rectum. Four of the 7 patients had objective responses and another 4 of the 7 received subjective benefit. The numbers are insufficient for a meaningful statistical analysis.

The lowest blood cell counts recorded during the therapy, in those patients who responded best to the treatment in the entire study, are shown in Tables IX, X and XI.

TABLE VIII

CARCINOMA OF RECTUM TREATED WITH COMBINATION OF DRUG AND RADIATION THERAPY

Patient	Dose of Drug (gm./days)	Radiation as Strandqvist Percentile	Results*
1	6.5/98	100	NI
2	3.0/40	66	S and O
3	2.4/30	100	S and O
4	1.5/3	53	O
5	23.5/30	76	NI
6	5.5/32	100	S
7	410/8	86	S and O

* S—subjective improvement; O—objective improvement; NI—no improvement.

When the figure for the drugs was added to the Strandqvist percentile and compared to result, it may be seen that 4 of 7 patients had objective responses and 4 of 7 patients benefited subjectively.

TABLE IX

MARROW TOXICITY: RECTUM, SUBJECTIVE AND OBJECTIVE IMPROVEMENT PATIENTS

Patient	MR	BI	CP
Lowest white blood cell count	2,300	4,200	2,100
Lowest platelets ($\times 10^3$)	81	85	101
Lowest hemoglobin (gm.)	11.0	13.0	11.1
Therapy*	F	RF	RF

* F—5-fluorouracil; RF—combined therapy.

TABLE X

MARROW TOXICITY: LARGE BOWEL, SUBJECTIVE AND OBJECTIVE IMPROVEMENT PATIENTS

Patient	WB	MB	CP	KC	WR	BR	EP	JMK	TM	HP	MC
Lowest white blood cell count	2,300	5,400	3,200	3,000	3,400	3,000	3,200	2,500	1,000	5,400	1,400
Lowest platelets ($\times 10^3$)	96	185	98	100	84	30	106	96	150	180	180
Lowest hemoglobin (gm.)	11.4	10.6	11.6	—	10.2	11.1	10.6	9.6	13.6	11.8	11.6
Therapy*	RF	F	F	F	F	RF	F	RF	RF	RF	F

* F—5-fluorouracil; R—radiation; RF—combined therapy of radiation and 5-fluorouracil.

Table XI

MARROW TOXICITY: STOMACH,
SUBJECTIVE AND OBJECTIVE IMPROVEMENT PATIENTS

Patient	LA	WD	JF	EP	AD	WC	IY
Lowest white blood cell count	5,000	1,900	4,300	3,350	3,500	5,600	6,500
Lowest platelets ($\times 10^4$)	13.6	9.5	13.9	14.5	10.3	14.0	10.4
Therapy*	F	RF	RF	F	RF	RF	F

* F—5-fluorouracil; RF—combined therapy of radiation and 5-fluorouracil.

It is seen that out of 21 patients with both objective and subjective improvement, only 4 did not show evidence of bone marrow depression. However, none of the remaining 17 patients showed clinical signs of platelet or white blood cell depression.

This would suggest that the degree of depression can be controlled by careful administration of therapy and withdrawal of it at an appropriate time. To obtain a good response to therapy production of hazardous toxicity is not necessary.

All patients in this series had varying degrees of gastrointestinal toxic symptoms (diarrhea, nausea, vomiting, stomatitis) but none of these were severe enough to necessitate permanent cessation of therapy.

One further correlative study was carried out to confirm the amount of radiation required, in terms of Strandqvist ratios, in those patients who had the same chance of improving as a result of radiation therapy, whether given alone, or by a combination of drug and radiation. The purpose of this study is a simple comparison of the amount of radiation required for a given good response. For this purpose a "t" test was carried out between the amount of radiation when used alone in terms of the Strandqvist curve values, *vs.* radiation when combined with a drug. This test demonstrated a p value of 0.002. Thus it is shown that there is a significant difference between the amount of radiation actually delivered to the patient when a drug is added; this is probably related to the degree of patient tolerance to two "toxic" modalities of treatment.

DISCUSSION

It has long been stated that some tumors are radiosensitive and others less so. The actual mechanisms involved in the phenomenon of sensitivity are incompletely understood, but are partly explicable in terms of enzymes generated by the cell itself during healing or recovery. The fact that there exists a positive relationship of correlation between dose and response when radiation is measured as Strandqvist ratios, rather than daily roentgen dosage, underlies an interesting fact that may be of clinical use when radiation therapists are referring to the amount of treatment actually given. Whether or not "sufficient" radiation has been delivered to a given tumor mass may more logically be expressed in terms of whether the ideal Strandqvist curve has been attained for a given volume field.

The fact that the statistical values proved significant for 5-fluorouracil therapy in carcinoma of the colon is also interesting in that colonic tumors are those which other studies have shown to be most amenable to treatment by this compound. The figures for stomach and rectum are too small for statistical analysis but the results appear to be encouraging with drug treatment in the stomach, but disappointing in rectal lesions.

The response achieved with combined radiation and 5-fluorouracil in colonic lesions is analyzed as being due to additive efficacy, but not synergism. There is no evidence from this study that results are better when drugs are used in combination

with radiation therapy; but we do suggest that when combination therapy is performed a good response is not jeopardized. It may be quite justifiable to add drugs to radiation when the amount of radiation has to be kept low (below ideal Strandqvist values) because of large field size, or where lesions are known to exist outside of this field and are thus not treatable by radiation therapy.

In general, the two forms of treatment can be combined without undue discomfort to the patient with the exception of the occasional one who develops diarrhea. In such a case one of the two modalities should be stopped, at least for a time; in our center usually the drug dosage is lowered or the drug discontinued to allow the patient's bowel function to return to normal. The same may be said concerning hematologic toxicity: the drug dosage is lowered or stopped if necessary to allow continuation of the radiotherapeutic management, but at the earliest opportunity is restarted in cautious amounts. It is hoped that this preliminary study may interest others to compile data of the same type so that definite conclusions can be made as to the actual worth of combination therapy in patients suffering from gastrointestinal malignancies.

SUMMARY

A series of patients with gastrointestinal malignancies have been studied from the viewpoint of evaluation of response to radiation, chemotherapy, and a combination of the two modalities. Evidence is presented to show that:

(1) There is a direct relationship between the amount of radiation delivered and tolerated and the response of the tumor itself. Radiation is best understood in terms of the Strandqvist curve relationships. A Strandqvist ratio is defined as that percentile level towards the ideal curve that has been attained for a specific patient.

(2) Combination of 5-fluorouracil and ionizing radiation produces the same response as radiation alone, provided the radiation is given in a sufficient amount. If not, the drug can act as a useful additive.

(3) The amount of radiation delivered is significantly less in those patients where drugs are employed in combination. The end results, however, demonstrate that addition of the drug to a lowered radiation dosage does not jeopardize the chance of the patient gaining a good result. Indications for combined therapy include patients where the field size is such that ideal Strandqvist values are difficult to achieve or in those patients where there is known disease outside the field of radiation.

(4) Responses have been measured in both subjective and objective categories; the majority of patients who feel better, do, in fact, show objective changes in tumor growth patterns. Anticancer treatments rarely make a patient feel better in a nonspecific manner.

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INTRA-ARTERIAL IRRADIATION OF CARCINOID TUMORS OF THE LIVER*

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THE aim of radiotherapy is to treat tumor and spare normal tissue. If the tumor is more vascular than the normal tissue around it, it should be possible to irradiate the tumor preferentially by the intra-arterial injection of radioactive material. Carcinoid tumor of the liver is such a lesion, and we have selected this tumor for evaluation of the effect of injection of yttrium 90 in microspheres into the hepatic artery in 5 patients.

Carcinoid tumors are not common, and the occurrence of carcinoid metastases of size and function sufficient to produce the carcinoid syndrome is rare. This syndrome causes bizarre manifestations and dramatic symptoms. It is initially difficult to diagnose and the syndrome may last for years. Many aspects of the carcinoid syndrome have been reviewed in detail in the literature recently.[8] Twenty-four patients with this disease are under study by one of us (RRPW) at The Mount Sinai Hospital in New York. In this series the syndrome of carcinoid manifestations has included: (1) vasomotor (cutaneous flushes, hypotensive crisis, renal failure); (2) gastrointestinal (diarrhea, cramps, vomiting, hypokalemia, malabsorption); (3) respiratory (bronchoconstriction); (4) cardiac (congestive heart failure, endocardial and valvular lesions); and (5) cutaneous (telangiectasia, pellagra, edema) changes.

In this disease the functioning tumor tissue produces large amounts of serotonin and vasoactive kinin peptides (bradykinin) which it releases into the circulation. Most of the manifestations of the syndrome are attributed to the pharmacologically potent effects of these substances. In rare cases, excesses of histamine are also found in the blood and urine.

Dietary tryptophan is the basic precursor from which the tumor forms serotonin. Tryptophan is to a large extent diverted from its normal metabolic pathways by the functioning tumor, hydroxylated to form 5-hydroxytryptophan, which is then converted into serotonin. This active amine is in turn largely converted to the pharmacologically inert metabolite 5-hydroxyindoleacetic acid (5-HIAA) and excreted in the urine where, in carcinoid syndrome, it is almost invariably found in markedly increased amount.

Unlike circulating levels of bradykinin, blood levels of serotonin and urine levels of 5-HIAA have correlated poorly with flushing attacks and other manifestations of the syndrome. However, in each individual case, progressive improvement or worsening over periods of several weeks or months appear to be associated respectively with decline or increase in serotonin and 5-HIAA values.

The liver is the most frequent site of distant metastasis from an intestinal primary of carcinoid tumor. These metastases are slow growing and slow developing. They may be solitary, but usually they are multinodular.

The roentgen characteristics of the liver

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metastases suggest that these tumors can be differentially irradiated via their arterial supply. Selective hepatic artery angiography shows relatively dense opacification of the metastatic tumors in the liver, and the masses are usually round, regular in border, and displace rather than invade the normal vascularity of the liver. When tumors are large, several cm. in diameter, their centers fail to opacify, the appearance being doughnut-like due to necrosis or avascularity of the center of the large metastasis. There may be a persistent stain on roentgenograms made late after injection of radiopaque material, and sometimes there are bizarre vessels within the lesion. We found no evidence of arteriovenous shunting within the tumors, and the hepatic venous drainage of the lesions was never visualized.

In a conventional hepatic scintiscan made after the intravenous injection of gold (Au^{198}) chloride colloid, the metastases appear as zones of decreased activity. This relative absence of radioactivity in the tumor indicates an absence of reticuloendothelial tissue in these masses. The gold scan correlates well with arteriographic findings.

Arteriography was performed by selective catheterization of the hepatic artery percutaneously through the axillary or femoral artery. In one instance, the catheterization was done at laparotomy through the left gastric artery.

The radiosensitivity of carcinoid tumor is low. The tumor is unusual, and no single experience is sufficient to determine its response to radiation.[1] At the same time, the symptoms, the carcinoid attacks, are so dramatic that a decrease in these attacks can be detected readily. Indeed, in one of our patients, decrease in the severity and frequency of carcinoid attacks followed external cobalt 60 teletherapy of a massive tumor of the liver.

For the intra-arterial irradiation of carcinoid tumors of the liver, we used carbonized microspheres* with beta emitting yttrium 90 incorporated within the microspheres. Yttrium 90 emits a beta particle with a maximum energy of 2 mev., and its half life is 2.6 days. The microspheres were 15 microns in diameter, and they were suspended in dextran.

* Minnesota Mining and Manufacturing Company, St. Paul, Minnesota.

TECHNIQUES OF INJECTION

Percutaneous catheterization of the hepatic artery under fluoroscopic image intensification control was made by the Seldinger technique through an axillary or femoral artery. Once the catheter was in the celiac artery, 35 ml. of renografin 76 was injected with a pressure syringe. Serial roentgenograms were obtained to map out the vascular anatomy of the upper abdominal viscera. The catheter was then manipulated into the main hepatic artery or into its branches which perfused the hepatic metastases. Angiography was performed to confirm the position of the catheter and to be sure that only the liver was being perfused. The suspension of Y^{90} was then mixed with renografin to make it radiopaque as it was slowly injected into the hepatic artery under fluoroscopic control. This slow injection is important to prevent reflux of the Y^{90} in the hepatic artery back into the celiac artery. A repeat angiogram was obtained directly after the injection of the isotope to confirm that the catheter had not moved.

Bremsstrahlung scans of the liver were made after the procedure to show the distribution of the radioactivity within the liver. In a previous report, we demonstrated the feasibility of using Bremsstrahlung scans to detect the presence of the beta emitting yttrium 90, and we have also shown that these scans can be used for aid in dosimetry.[3,4,5,6]

The Bremsstrahlung scans are made of the lungs as well, to search for evidence of "leakage" of the isotope through the liver or tumor into the general circulation. Although such leakage does occur when the arterial vessels of some other organs are injected, no Y^{90} is detectable in the lung after the injections of microspheres of Y^{90} into the hepatic artery.

COMPLICATIONS AND DIFFICULTIES

The main technical problems in the procedure are the catheterization of the hepatic artery or its branches and the avoidance of injecting radioactive material into normal tissues. If the Y^{90} enters the wrong vessel, its presence in another organ can be determined by Bremsstrahlung scanning. In this respect, there is considerably more information on the distribution of radioactive isotopes than is available in the case of similar procedures using chemotherapeutic agents administered intra-arterially. At times it is technically difficult to get into the proper artery, but only once in our series were we completely unable to enter the hepatic artery. If catheterization is done at laparotomy, there should be more control of the exact distribution of the isotope. Before injection of radioactive material, the distribution of the vasculature can be evaluated by injecting fluorescent dye, and undesired arteries can be temporarily clamped off. However, in our experience, percutaneous catheterization of the hepatic arteries is more effective, easier on the patient, less complicated and safer if all precautionary techniques are exerted.

Maldistribution of the radioactive material is possible, and unintentional irradiation of the stomach has occurred in 2 of our cases. In one instance this developed at laparotomy, probably because one or more branches of the injected artery were not visualized. The second case occurred following percutaneous catheterization because the tip of the catheter moved between the time of the angiogram and the actual injection of Y^{90}. In this instance a large dose of radiation was administered to the lesser curvature of the stomach resulting in a huge flat ulceration (Case III).

REPORT OF CASES

CASE I. The Mount Sinai Hospital #326958 (MA). A 67 year old businessman had had a carcinoid tumor of the small bowel and root of the mesentery 2 years previously. At operation, nodules were palpated in the liver. Episodes of carcinoid attacks including flushes, diarrhea and prostration were treated by opiates, chlorpromazine, potassium and methysergide. After treatment, the carcinoid attacks were less frequent and less severe, but the relief was only temporary. On the return of the severe attacks, the patient was admitted to The Mount Sinai Hospital in June, 1966, for intra-arterial irradiation. A preliminary liver scan with gold (Au^{198}) colloid showed several large "cold" areas in the liver, indicating metastases. A common hepatic arteriogram was obtained by passing a catheter percutaneously through the left axillary artery. Opacification of the common hepatic artery and liver showed multiple round tumor strains, varying from 1 cm. to 5 cm. in diameter. The larger masses had avascular or necrotic centers.

After arteriography had shown the catheter to lie in the desired common hepatic artery, a 3 ml. suspension of plastic microspheres containing 15 mc of Y^{90} was injected into the catheter. The catheter was then removed, and manual compression on the left axillary artery was maintained for 20 minutes. The following day, a Bremsstrahlung scan of the liver showed the radiation restricted to the liver; the metastases had relatively increased uptake of the intra-arterially injected Y^{90}.

The patient tolerated the procedure well, and he was discharged on the day following the injection. His carcinoid attacks again subsided in severity about one week later. The dose of radiation to the liver from the 15 mc of Y^{90} was estimated to be 2,500 rads (Fig. 1).

Six months later (January, 1967), the patient developed severe lower abdominal pain and recurrent flushing which were considered due to regrowth of tumor with retroperitoneal lymph node involvement. The lower abdomen was treated with external radiation by moving-strip cobalt 60 teletherapy,[7] but the pain and the flushing were unrelieved.

Comment. The dose of radiation by intra-arterial Y^{90} was limited to 2,500 rads, and this dose resulted in definite decrease in the severity and frequency of the carcinoid attacks for 6 months.

CASE II. The Mount Sinai Hospital #246155 (SS). A 50 year old housewife had a known abdominal carcinoid tumor for more than 4 years during which time she had weight loss and frequent episodes of flushing and diarrhea. In 1961, a needle biopsy of a liver mass revealed car-

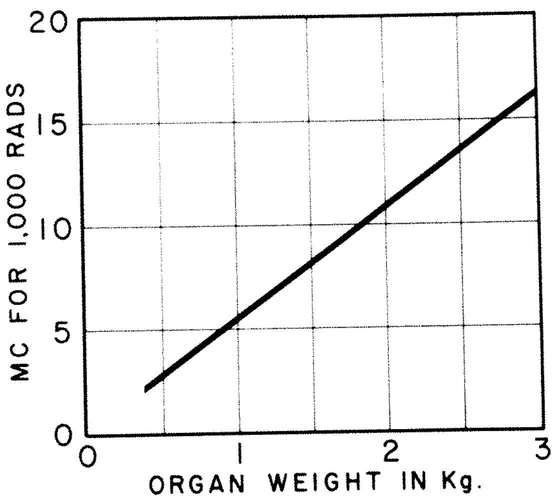

Fig. 1. Yttrium 90 dosimetry. Dose of radiation absorbed in liver after intra-arterial injection of microspheres containing Y^{90} is determined by the formula:

$$D_B = 73.8 C E_B T,$$

where D_B = dose from beta particles, C = concentration of isotope in microcuries per gram, E_B = average energy of beta particle (0.93 mev. for Y^{90}) and T = half life in days (2.6 for Y^{90}). The formula assumes even distribution of the isotope and no leakage of microspheres from the liver. The weight of the normal liver is assumed to be 1,500 grams.

cinoid tumor. In 1964 at laparotomy, a catheter was inserted into the common hepatic artery, and it remained in place for 5 months while 5FU and later 5FUdR were administered by constant intra-arterial infusion via a miniaturized portable pump. The palpable masses decreased in size and her symptoms improved, but the catheter broke and retracted into the abdomen terminating the treatment. When the liver again enlarged, external cobalt 60 teletherapy was administered anteriorly to the right lobe of the liver through a 12×12 cm. portal for a dose of 3,000 rads. The mass appeared to shrink from this treatment also, but the liver again enlarged, and the carcinoid attacks became more severe. She was admitted to The Mount Sinai Hospital on February 9, 1966, for intra-arterial irradiation. A gold (Au^{198}) colloid scan of the liver showed huge "cold" areas in the right lobe. A catheter was inserted into the right hepatic artery via a percutaneous left axillary artery puncture. After the arteriogram showed the catheter to lie in the right hepatic artery, 50 mc Y^{90} in plastic microspheres was injected into the liver. A subsequent Bremsstrahlung scan showed increased uptake of the isotope in the large metastases previously demonstrated as voids in the gold scan. No activity was detected over the left lobe of the liver.

Directly following the intra-arterial injection of Y^{90}, the patient had exacerbation of her carcinoid symptoms, but these subsided in about 1 week, and the patient went on to an even more satisfactory response than she had experienced with the previous intra-arterial chemotherapy. The estimated weight of the portion of the liver injected with Y^{90} was 3,000 gm. The dose to the liver from the 50 mc of Y^{90} was 3,100 rads (Fig. 1).

About 10 months later (January 1967), the masses rapidly increased in size again and the carcinoid symptoms returned to their former severity. On February 16, 1967, the right hepatic artery was once more catheterized percutaneously. Angiography demonstrated the metastatic deposits in the liver, and 40 mc of Y^{90} was injected into the right hepatic artery. There were 2,300,000 microspheres per ml., and 4 ml. were injected (10 mc Y^{90} per ml.). The estimated dose to the liver was 2,500 rads. The patient tolerated the procedure well and a Bremsstrahlung scan of the liver showed the activity in the right lobe. Again the patient had early exacerbation of her symptoms, followed by 6 months of remission. Thereafter, carcinoid attacks of great severity recurred, and, after 3 months, she succumbed to acute renal insufficiency due to a prolonged hypotensive crisis during a severe carcinoid attack.

Comment. The symptoms of carcinoid in this patient were relieved by intra-arterial chemotherapy administered over a 5 month period, but they were similarly relieved by the simpler process of a single intra-arterial injection of Y^{90}. Also, in the radiation procedure, the isotope was injected percutaneously; an exploratory laparotomy was not required.

Case III. The Mount Sinai Hospital #285388 (HB). This 46 year old woman had a transverse colectomy 4 years previously for adenocarcinoma of the transverse colon, and carcinoid metastases from an undetermined primary lesion were surprisingly encountered in the

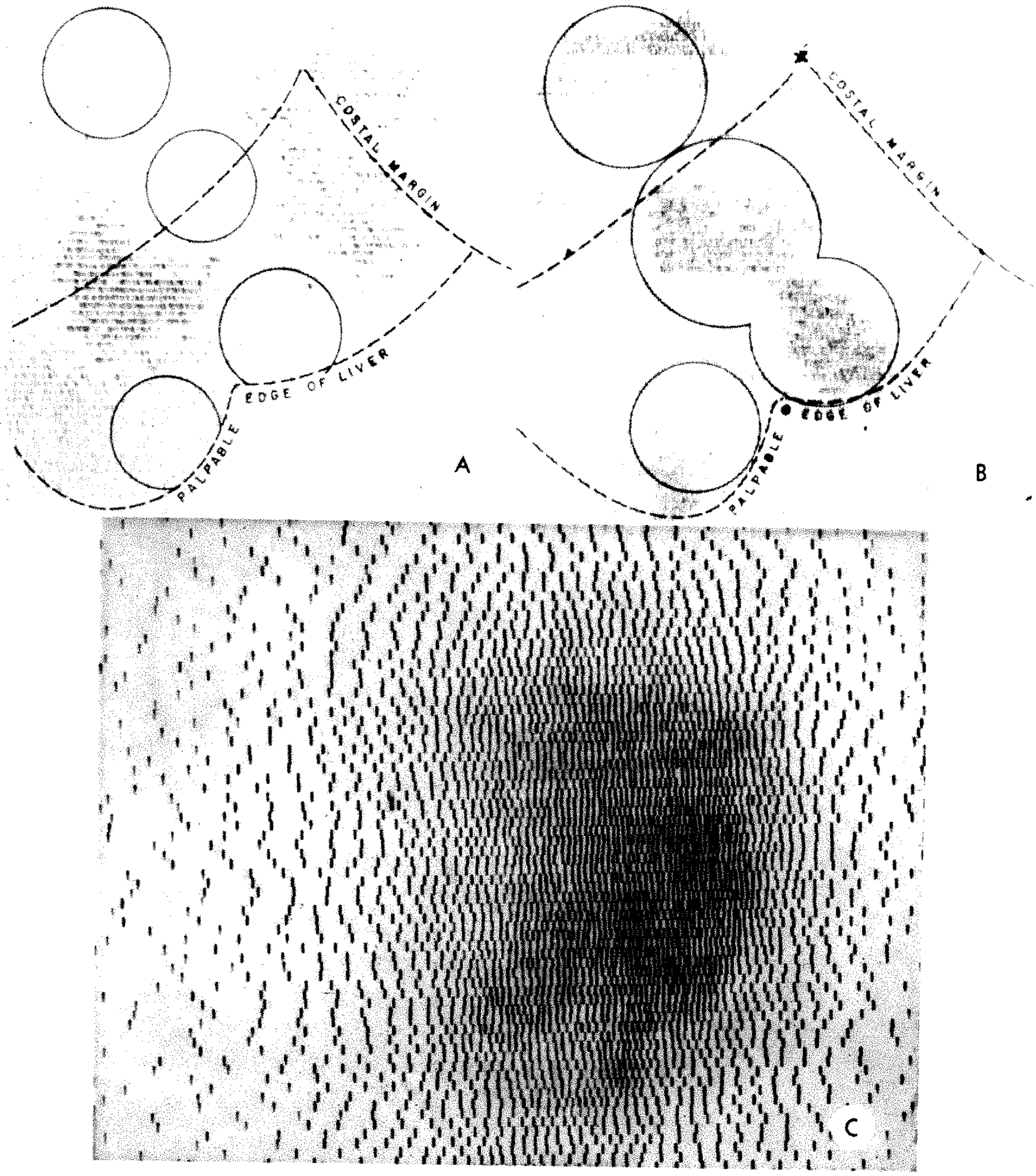

FIG. 2. Case III. (*A*) Scintiscan of liver using gold (Au^{198}) colloid showing voids or "cold" areas representing the carcinoid metastases. (*B*) Bremsstrahlung scan showing the distribution of the Y^{90} after injection into the right hepatic artery. The hypervascular carcinoid deposits are "hot" containing more of the Y^{90} than normal hepatic tissue. It is of interest that the left lobe of the liver contains no detectable Y^{90}. (*C*) Bremsstrahlung scan of liver following second procedure shows activity localized on the left, the Y^{90} having been injected unintentionally into the left hepatic and left gastric arteries. (*A* and *B* reproduced by permission from *Radiology*.)

liver. One year previously (June, 1965), intra-arterial 5FU was injected into the hepatic artery for 5 days, but the patient went into profound shock and this therapy had to be stopped. After several weeks of severe exacerbation of carcinoid attacks, she had considerable improvement with shrinkage of her liver which lasted about 9 months. In June, 1966, her attacks and congestive heart failure from carcinoid (tricuspid insufficiency) heart disease became so severe that she was admitted to The Mount Sinai Hospital for intra-arterial catheterization with Y^{90}. Through a percutaneously placed right hepatic artery catheter, 33 mc of Y^{90} was injected into the right lobe of the liver, after a gold scan (Fig. 2, *A* and *B*) showed huge masses. Estimating the weight of the liver containing the Y^{90} to be 2,000 gm., the radiation dose was 3,000 rads. No beneficial effect was obtained, and the patient's general condition was worsening critically. Two months later (September 1966) the procedure was repeated, this time with the injection of 40 mc of Y^{90}, again presumably into the right hepatic artery. However, a Bremsstrahlung scan following this procedure showed the activity to be localized on the left (Fig. 2*C*); the radioactive material had been injected unintentionally into the left hepatic and left gastric arteries, rather than into the right hepatic artery. The stomach received an estimated dose of several thousand rads along its lesser curvature, and roentgenographic examination of the stomach showed a large flat ulceration along the distribution of the activity in the Bremsstrahlung scan and, correspondingly, along the course of the left gastric artery (Fig. 2*D*). The patient's course was rapidly downhill, with severe abdominal pain, vomiting, occasional hematemesis, intractable heart failure and continued carcinoid attacks.

Fig. 2. (*D*) Large ulcer of the lesser curvature of the stomach, probably due to microspheres containing Y^{90} in the distribution of the left gastric artery.

Comment. Despite care, it is possible for the catheter to be displaced between the time of developing the rapid-sequence arteriograms and the injection of the Y^{90}. In this instance, in the second procedure, the angiogram had demonstrated filling of the right hepatic artery, but after the injection of Y^{90}, the Bremsstrahlung scan showed the radioactive material to be in the left side of the liver and the stomach. The branches of the celiac axis are varied, and these anatomic variations require utmost care in prevention of moving a well placed catheter while awaiting successive steps in this intra-arterial procedure. This is especially true when the liver is greatly enlarged as the arterial branches are then displaced and distorted and may be difficult to identify. The large ulcer in the lesser curvature of the stomach was most likely induced by the radiation, although some observers have proposed that it may represent a "shock" ulcer. Now, in order to avoid injection of the radioisotope into the wrong artery, we mix the microspheres with the radiopaque contrast material, and we watch the flow of the mixture fluoroscopically. In this way we hope to stop the injection promptly if the flow is not in the intended artery.

Case iv. The Mount Sinai Hospital #407526 (SB). A 19 year old premedical student had been having episodes of warm feelings and facial flushing for 3 years. More recently he experienced attacks of palpitation, actual syn-

cope and constricted breathing and weight loss. He was diagnosed as having carcinoid syndrome at the Long Island Jewish Hospital, and a gold scan there (Fig. 3*A*) showed metastases in the liver. At The Mount Sinai Hospital on March 7, 1967, a catheter was introduced percutaneously via the right axillary artery and advanced into the right hepatic artery. An arteriogram verified the presence of multinodular hypervascular metastases in the right lobe of the

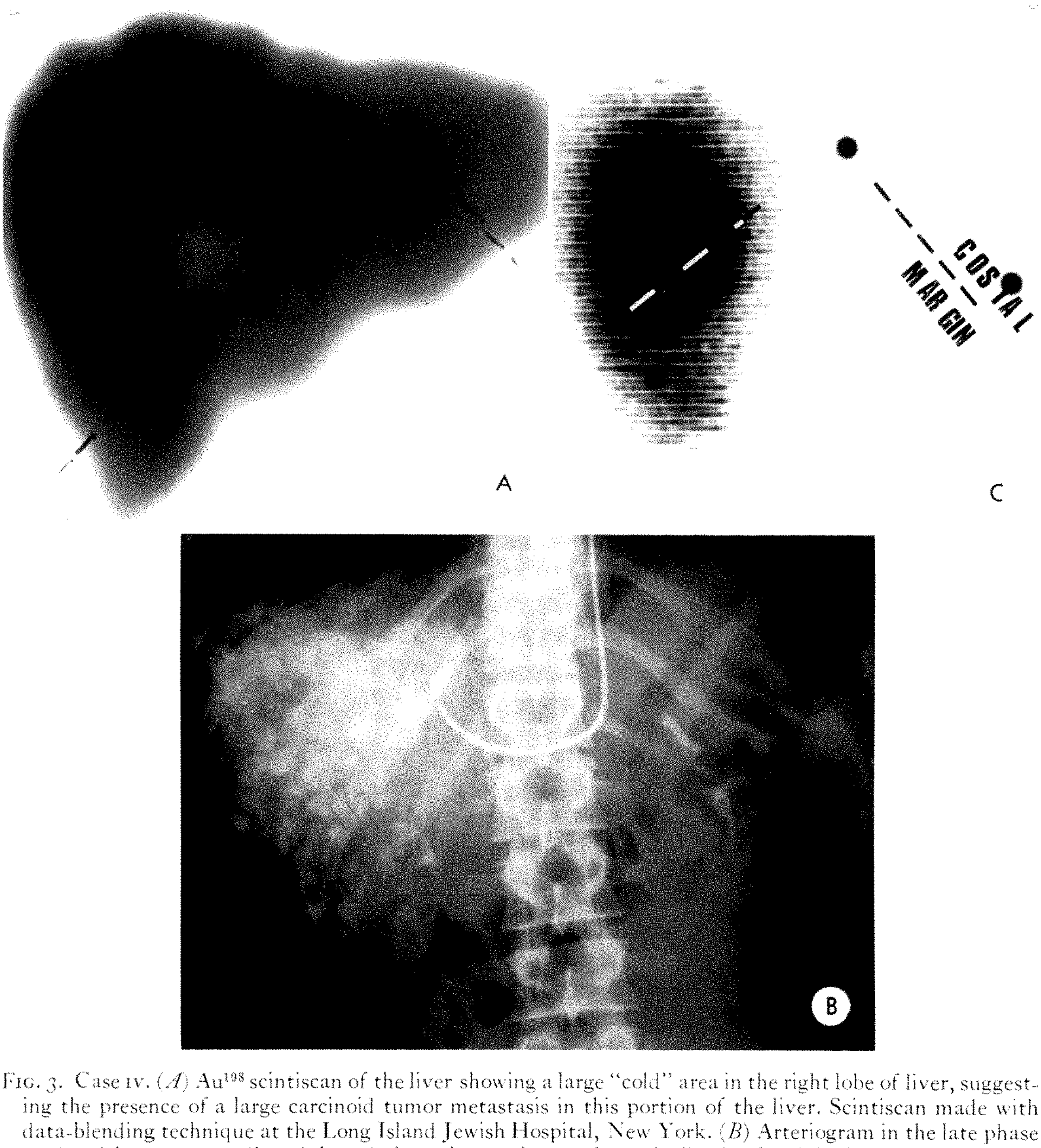

FIG. 3. Case IV. (*A*) Au^{198} scintiscan of the liver showing a large "cold" area in the right lobe of liver, suggesting the presence of a large carcinoid tumor metastasis in this portion of the liver. Scintiscan made with data-blending technique at the Long Island Jewish Hospital, New York. (*B*) Arteriogram in the late phase made with opaque medium injected through a catheter whose tip lies in the right hepatic artery. The catheter was introduced percutaneously via the left axillary artery. There are numerous hypervascular metastases grouped around a single large tumor whose center is necrotic, a finding often seen in carcinoid tumor metastatic to the liver. This arteriogram verified the position of the catheter to be correct for the injection of Y^{90} into the right hepatic artery. (*C*) Bremsstrahlung scan of liver after injection of Y^{90} into right hepatic artery shows satisfactory concentration of isotope in region of metastases in the right lobe of the liver.

liver, the largest about 6 cm. in diameter (Fig. 3*B*).

Following the arteriogram, 30 mc of Y^{90} in plastic microspheres suspended in 4 ml. of dextran solution was injected into the hepatic artery. A Bremsstrahlung scan verified the location of the activity in the right lobe of the liver and showed increased uptake of the Y^{90} in the actual metastases as compared with adjacent liver (Fig. 3*C*). The day after the procedure, the patient was discharged from the hospital to go back to college, without side effects. Since discharge his course has been smooth with improvement in symptoms and weight gain. His blood cell count remained normal.

Comment. When a patient is in relatively good general condition, this procedure of hepatic arteriography and injection of Y^{90} in plastic microspheres is well tolerated and without significant morbidity.

Case v. The Mount Sinai Hospital #349495 (CS). A 40 year old single woman had had flushing attacks from early childhood. Her elevated blood serotonin levels and increased urinary 5-HIAA indicated the diagnosis of carcinoid syndrome, but no actual deposit of tumor was known until recently, when a gold scan of the liver suggested the presence of metastases. Abdominal exploration was decided upon to provide a tissue diagnosis and to determine the extent and sites if involvement. On January 23, 1967, surgical exploration revealed numerous yellow, firm nodules on the surface of the liver, varying in size from a few mm. to 2 cm. in diameter. In addition, multiple masses of carcinoid tumor were found in the ovaries and in the mesentery near the appendix, all of which were resected. A catheter was then inserted into the right gastroepiploic artery and advanced into the hepatic artery. Injection of fluorescein into the catheter and inspection under ultraviolet light showed yellow fluorescence of the surface of the liver, and the position of the catheter was presumably satisfactory for the intra-arterial injection of Y^{90}. Tiny 1×6 mm. cylindrical dosimeters of lithium fluoride in teflon were inserted into representative portions of normal liver and metastases to determine the relative dose in tumor and normal liver (Fig. 4). The 2.2 ml. of microspheres containing 22 mc of Y^{90} were injected into the liver for a planned dose of 3,000 rads. The LiF dosimeters in the normal liver and in the metastases indicated that the dose of radiation in the tumors was about twice the dose in the normal liver.

Bremsstrahlung scan of the liver postoperatively showed considerably more uptake in the left lobe of the liver and stomach than was predicted or anticipated from the visualized fluorescence at operation. Subsequently, the patient developed gastric symptoms, and roentgenographic signs suggested significant irradiation of the stomach. Three months following surgery the patient died from massive upper gastrointestinal hemorrhage. Autopsy was not performed.

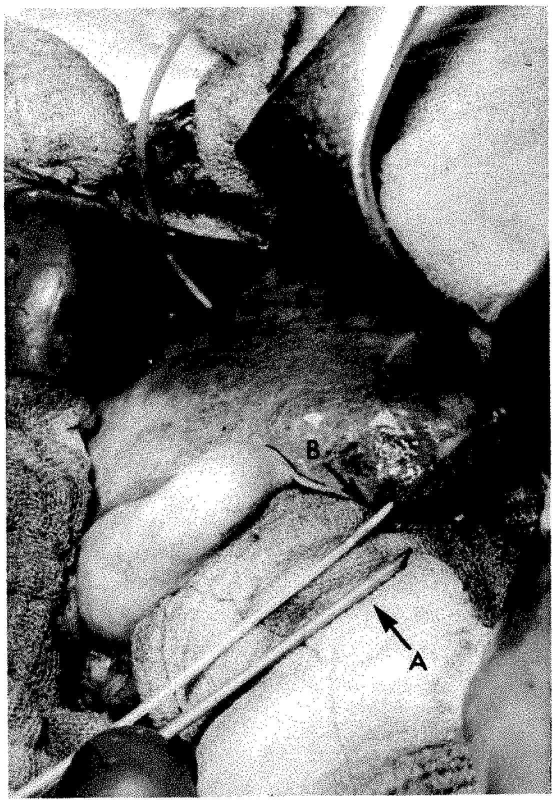

Fig. 4. Case v. At laparotomy lithium fluoride dosimeters* were inserted into normal liver and tumor. The hollow needle (A) used to insert the plastic sheathed dosimeters (B) is shown. Dosimeters within tumor nodules (C) received about twice the dose received by dosimeters within normal liver tissue. The dosimeters remained in the tissue for almost 1 hour after the Y^{90} had been injected into the hepatic artery.

* Controls for Radiation, Incorporated, Cambridge, Massachusetts.

Comment. In our series, this is the only liver we have injected at open operation. It was technically more difficult to catheterize the hepatic artery under direct inspection and palpation than percutaneously. Also, radioactive material did not distribute itself in exactly the same pattern as the fluorescence. In the evaluation of the distribution of an injection into the hepatic artery, observation of fluorescence under ultraviolet light seems less exact than scanning the distribution of injected Y^{90}.

DISCUSSION

Selective catheterization and angiography of the hepatic artery are procedures with little morbidity, and they provide both diagnostic information and a pathway for therapy. Tumors of the liver can be diagnosed by arteriography, and can be treated with intra-arterially injected radioactive material as part of the same procedure. Carcinoid tumors causing the carcinoid syndrome are peculiarly suited to this therapeutic approach, for they frequently metastasize to the liver.[2] They do not respond well to any known treatment and are ultimately fatal. Furthermore, therapy in these cases is realistically intended to impair function (humoral production) of the tumors and thereby palliate. It is futile to attempt total obliteration of the neoplasm. The palliative approach is logical since most patients with carcinoid syndrome eventually die from some complication of the pharmacologic activity of these slow growing tumors rather than directly from the growth and spread of the tumor itself. The carcinoid syndrome and a positive gold scan of the liver are adequate guides to the diagnosis of carcinoid tumor of the liver. Although the carcinoid tumor itself is not highly responsive to irradiation, our experience with intra-arterial irradiation indicates that the serious signs and symptoms of this disease can be palliated with little morbidity when the radioactive material is injected into the liver only, with none reaching the stomach. The pitfalls related to technique must be avoided to make sure the radiation only affects the desired tissue. Scanning of Bremsstrahlung is an adequate measure for localizing the distribution of the isotope, but it is a slow process (hours) as performed with a conventional rectilinear scanner. Therefore, we only made Bremsstrahlung scannings *after* the procedure was completed. It would be of advantage to use a rapid imaging device, such as a gamma camera, to show the distribution of a preliminary injection of a smaller than therapeutic amount of Y^{90}, or a test amount of a gamma emitter, before injecting the final and complete dose of Y^{90}. It is also prudent to keep dose levels low until better understanding of dosimetry and effect of radiation on the liver is achieved.

DOSIMETRY

For practical purposes, we assume that the intra-arterially injected beta emitter is distributed evenly throughout the liver and estimate the dose by the formula:

$$D_B = 73.8CE_BT,$$

where D_B = dose from beta particles, C = concentration of isotope in microcuries per gram, E_B = average energy of beta particle (0.93 mev. for Y^{90}), and T = half life in days (2.6 for Y^{90}). For convenience, the dose in rads for estimated tissue weights is shown in Figure 1. Another source of error in this dose determination is in the estimation of the weight of the tissue, the liver in this instance.

Because of these difficulties we have attempted to determine the dose with direct measurements. In Case v LiF dosimeters in the liver indicated doses within the tumor to be about twice the dose in the normal liver tissue. Samples of liver were removed for assay in a well counter and these showed doses of 1,700 rads in liver and 4,200 rads in tumor. The inhomogeneity of dose in tumor and normal liver may provide us with a significant safety factor, for there appears to be an appreciable preferential "uptake" of radioactivity in carcinoid tumors in comparison with normal liver.

SUMMARY

We have treated 5 patients with functioning carcinoid tumors of the liver by injecting Y^{90} in microspheres into the hepatic artery. This procedure has low morbidity, if extreme care is taken and there is no spillage of the injected material into the arteries of adjacent organs.

Palliation of the severe manifestations of the carcinoid syndrome follows this treatment and makes the therapy worthwhile.

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The authors thank the late Sergei Feitelberg, M.D., Physicist, The Mount Sinai Hospital, New York for his guidance in dosage determinations.

Thanks to Albert Cornell, M.D. for Case v whom he initially diagnosed and referred to the study group.

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GUIDED PERCUTANEOUS ARTERIAL INFUSION CHEMOTHERAPY*

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THIS communication describes a percutaneous catheter technique for arterial chemotherapy of tumors of diverse anatomic location. It is based upon a limited but continuous series of 12 adult patients. By this method, catheter exploration angiographically locates the optimum position for tumor infusion and a carotid or axillary insertion site permits patient ambulation (Fig. 1). It is not the intention of the authors to evaluate the pharmacologic results of chemotherapeutic agents used.

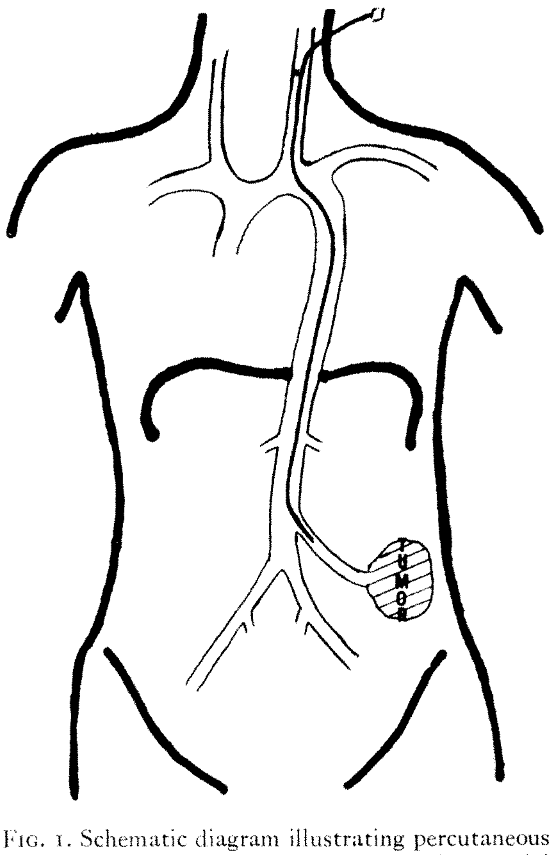

FIG. 1. Schematic diagram illustrating percutaneous catheter transcarotid approach to selective arterial infusion chemotherapy of an abdominal neoplasm.

In common practice, arterial infusion chemotherapy has been accomplished by inserting tiny catheters into selected arteries which have been exposed at surgery.[1,3,5,6,8] Adequacy of tumor perfusion is then estimated by the appearance of fluoroscein or methylene blue injected into the tumor area through the catheter.[2,3,8] Investigators who advocate the surgical approach express the opinion that angiography may be helpful but is not as direct evidence of adequate perfusion of the tumor as are dye tests.[8] However, it appears that the use of tiny catheters such as PE-50 and PE-90, inserted at open surgery,[8] do not permit adequate angiography. This is primarily due to inadequate flow rate of the opaque medium through these small catheters. Moreover, with the dye injection method, only the surgically visible portion of the tumor serves as a criterion for perfusion of the entire tumor mass. In addition, surgical isolation of tumor "feeder arteries" in large or extensive tumors may prove extremely difficult or impossible. Obstruction and displacement of tiny catheters, surgically placed, are also reported as a common problem with the open surgical approach.[8,9]

It has been cited that angiography does not always indicate the source of tumor blood supply, since a supply may be provided by an artery which is not opacified by angiography.[2] This pitfall may be obviated by the use of preliminary aortography at the tumor area, as will be demonstrated later. Finally, evidence of significant tumor perfusion by adequate selective angiography would seem to be of practical

* Presented at the Sixty-eighth Annual Meeting of the American Roentgen Ray Society, Washington, D.C., September 26–29, 1967
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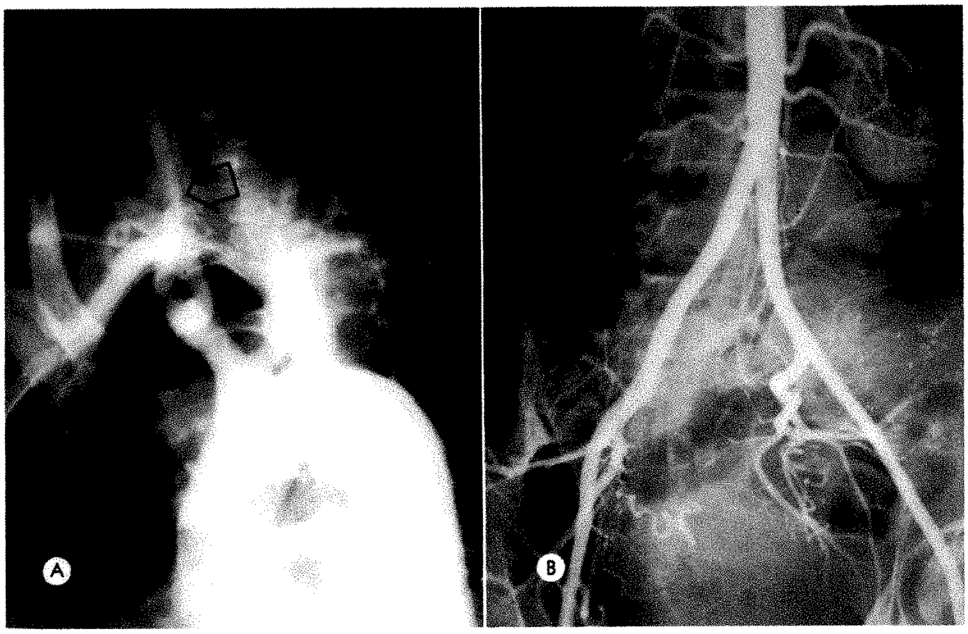

Fig. 2. Case 1. A 43 year old female with recurrent rectal carcinoma 2 years after abdominoperineal resection. (*A*) Preliminary transfemoral catheter aortography at aortic arch level indicates that the right carotid artery (arrow) provides the most direct carotid route to the pelvis for insertion of "chemotherapy catheter." (*B*) Aortoiliac angiogram indicates arterial anatomy of pelvic vessels which will be angiographically explored with the "chemotherapy catheter."

clinical value in a technique which is generally used for the palliation of malignant disease.

This experience indicates that percutaneous polyethylene catheters of moderate size* are well tolerated for a period of 2 to 3 weeks. These catheters allow adequate angiography for the determination of the catheter position which produces optimum tumor perfusion. The same catheter may then be left in place for continuous infusion chemotherapy. A roentgenogram will suggest possible displacement of the catheter tip during therapy if this question arises. If in doubt, an injection of opaque medium through the catheter will indicate its exact position.

The use of a carotid or axillary catheter insertion site allows comfortable patient ambulation during continuous arterial chemotherapy treatment. This report involves 8 carotid and 4 axillary percutaneous arterial insertion sites. With one exception, we have limited the carotid insertion site to younger patients (under the age of 45 years) because of the potential hazard of cerebral damage in older individuals who may have a borderline cerebral circulation. However, in all cases, a preliminary catheter arch aortogram provides a "road map" for selection of the most appropriate vessel for insertion of the "chemotherapy catheter."

* The B-D X .039 polyethylene catheter, I-D .039", O-D .079" and the Cook polyethylene catheter, I-D .032", O-D .070", have proved highly efficient in this experience.

TECHNIQUE

The technique consists of two basic steps: (1) Preliminary aortography; and (2) "chemotherapy catheter" insertion.

1. *Preliminary aortography*—using a single transfemoral catheter in two locations:
   (A) At aortic arch level—to evaluate arterial status and to select the appropriate carotid or axillary artery for insertion of the "chemotherapy catheter" (Fig. 2*A*; 5*A*; 7*A*; and 8*A*).

(B) At tumor level—to identify arterial anatomy in the tumor area (Fig. 2*B*; and 5*B*).

2. "*Chemotherapy catheter*" *insertion*—into the appropriate carotid or axillary artery:

(A) The catheter is directed to the tumor area (Fig. 3*A*).

(B) Vessels which may be tumor "feeders," based on a preliminary aortogram, are angiographically explored for optimum catheter position (Fig. 3, *B*, *C* and *D*; 6, *A* and *B*; 7, *B* and *C*; and 8*B*).

(C) The catheter is immobilized to the neck (carotid insertion) or

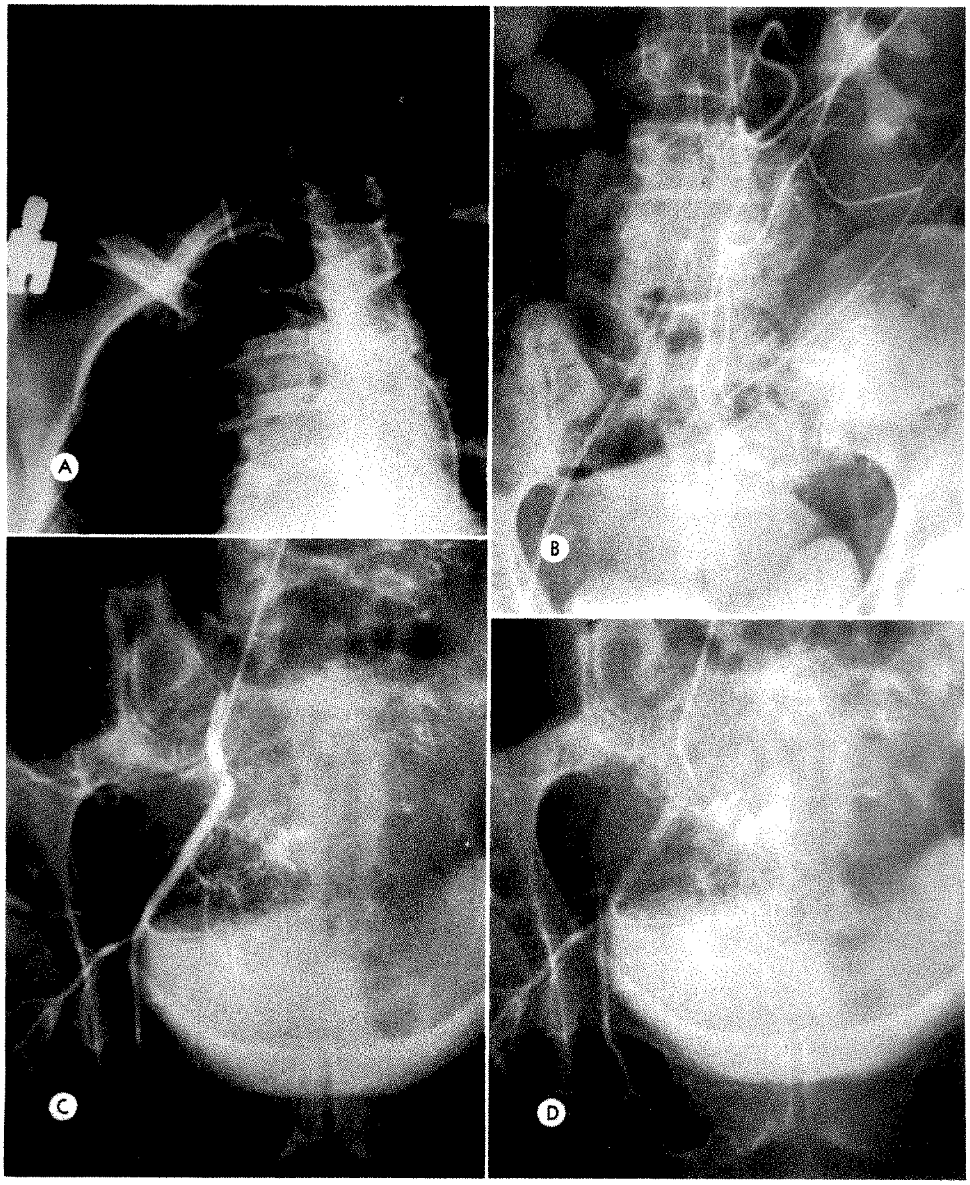

Fig. 3. Case 1. (*A*) Percutaneous right carotid "chemotherapy catheter" has been passed down the aorta. (*B*) Selective inferior mesenteric arteriogram with right transcarotid "chemotherapy catheter" indicates no tumor perfusion. Abrupt termination of hemorrhoidal branches of this artery is probably due to ligation at prior surgical resection. (*C* and *D*) Tumor vessel perfusion is shown by selective angiography of the right internal iliac artery. The catheter was left in this position for 19 days of infusion chemotherapy.

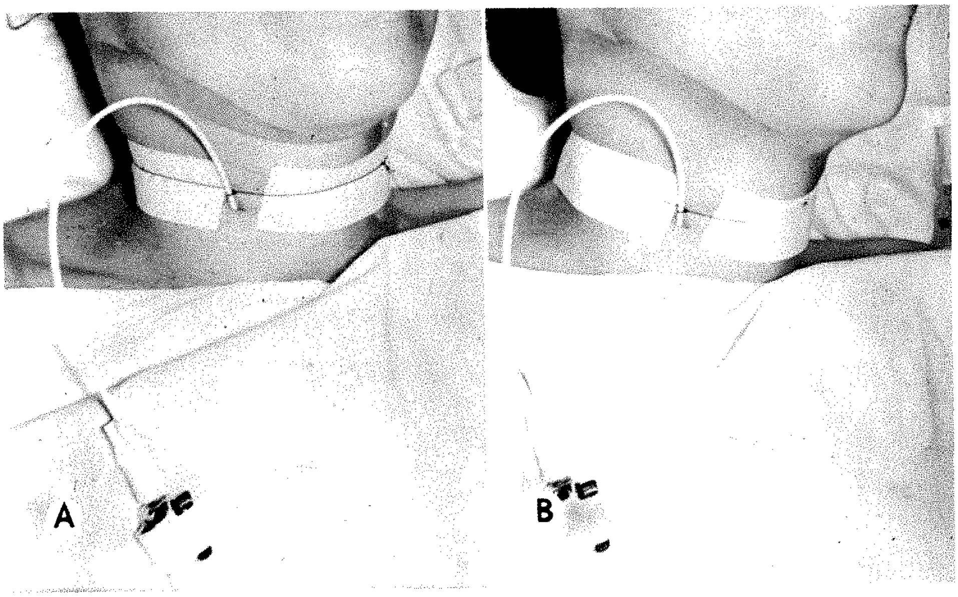

FIG. 4. Case 1. (*A*) The "chemotherapy catheter" is secured to the neck by tying over an adhesive band. (*B*) A second adhesive band covers the first and immobilizes the tie suture.

shoulder (axillary insertion) (Fig. 4, *A* and *B*; and 7, *D* and *E*) and is then attached to an arterial pressure pack or pump for chemotherapy.

COMPLICATIONS

In this series of 12 cases, a single case of cervical cellulitis complicated the carotid artery insertion area on the 6th day of chemotherapy. Chemotherapy was temporarily interrupted and, after 36 hours of antibiotics, the infection was controlled and chemotherapy was reinstituted. During the febrile period, the catheter was kept patent with continuous slow saline pressure drip. Treatment was then continued for an additional 16 days when chemotherapy was abandoned due to a progressing leukopenia.

No thromboses or bleeding problems were encountered during therapy. Even though these catheters remained in the carotid or axillary puncture site for periods up to 21 days, moderate local pressure for 5 to 10 minutes produced hemostasis after catheter withdrawal in all cases. In no instance was premature catheter removal necessary because of arterial complications or catheter occlusion. In all of these cases, the catheter was left in place until signs of systemic drug toxicity (principally leukopenia) occurred.

One case of right hemiplegia complicated withdrawal of a left carotid catheter in a 43 year old female but disappeared within 1 hour, with no neurologic sequelae. On two occasions, catheter occlusion was suspected but slight movement of the catheter tip restored free flow of the infusate. Injection of opaque medium at fluoroscopy indicated that the catheters had remained in proper position for tumor perfusion.

No other complications were recognized in this experience.

RESULTS

All patients were relatively comfortable and ambulatory except the one described above, who encountered considerable discomfort over a 36 hour period due to a complicating cellulitis which developed near the catheter insertion site in the neck. The manner in which the catheters were immobilized allowed free motion (Fig. 4, *A* and *B*; and 7, *D* and *E*).

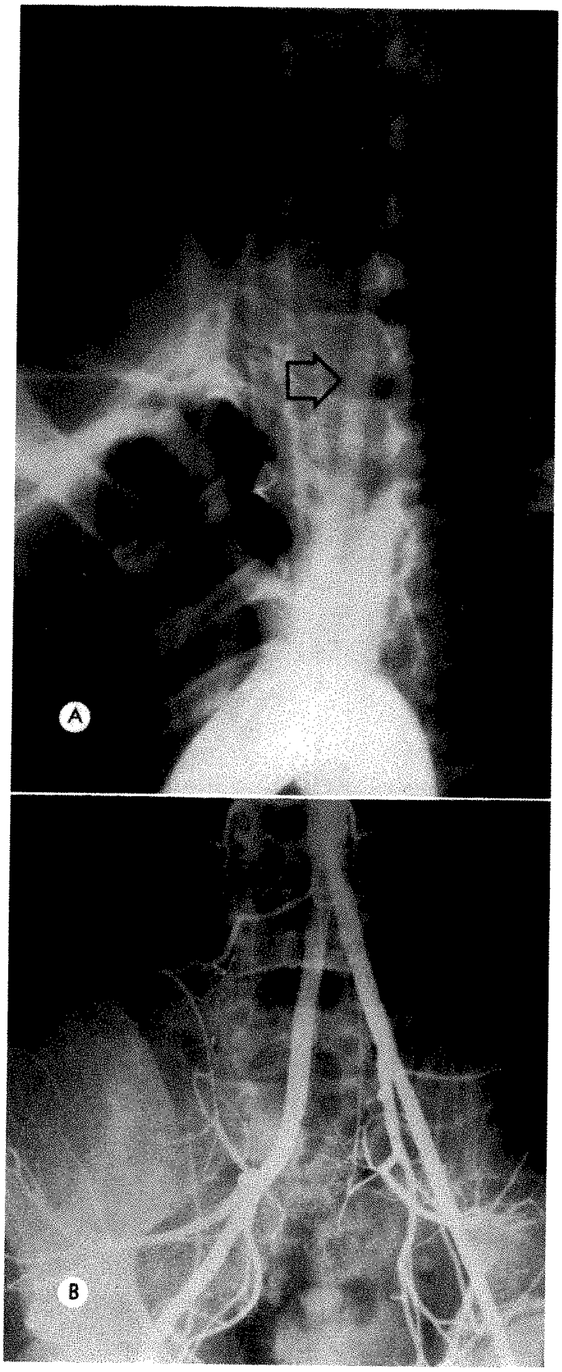

Fig. 5. Case II. Preliminary transfemoral catheter aortogram in a 36 year old male with chondrosarcoma of the right ilium. (*A*) Arch aortogram indicates that the left carotid artery (arrow) is an appropriate insertion site for the "chemotherapy catheter" which will be passed down the aorta to the pelvis. (*B*) Aortoiliac angiogram showing pelvic arterial anatomy.

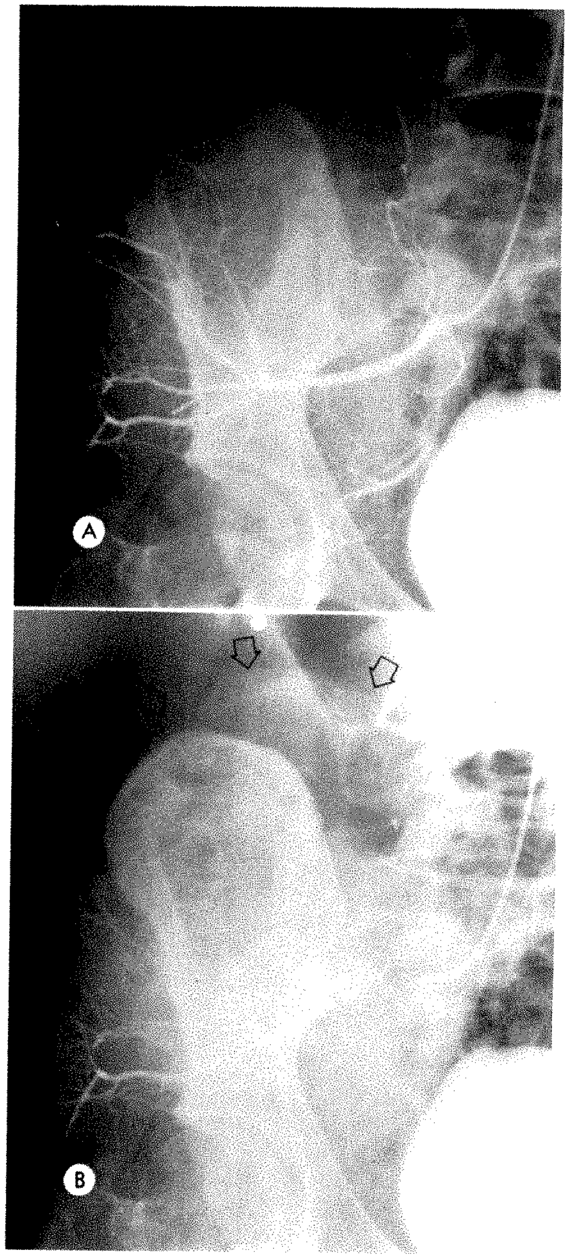

Fig. 6. Case II. (*A* and *B*) Tumor vessel perfusion (arrows) is shown by selective "chemotherapy catheter" angiography of the right superior gluteal artery. The catheter tip was left in this position and continuous infusion chemotherapy was administered for 17 days.

Some authors favor the use of pumps to maintain pressure for arterial infusion chemotherapy.[4,7] In this series, simple arterial pressure packs were used rather than pumps and seemed to function quite efficiently.

Although it is not the intention of this communication to discuss clinical results of chemotherapy, it is of interest that 4 patients showed a clinically beneficial response to the infusion treatment.

SUMMARY AND CONCLUSIONS

(1) A percutaneous catheter technique for arterial infusion chemotherapy is described.

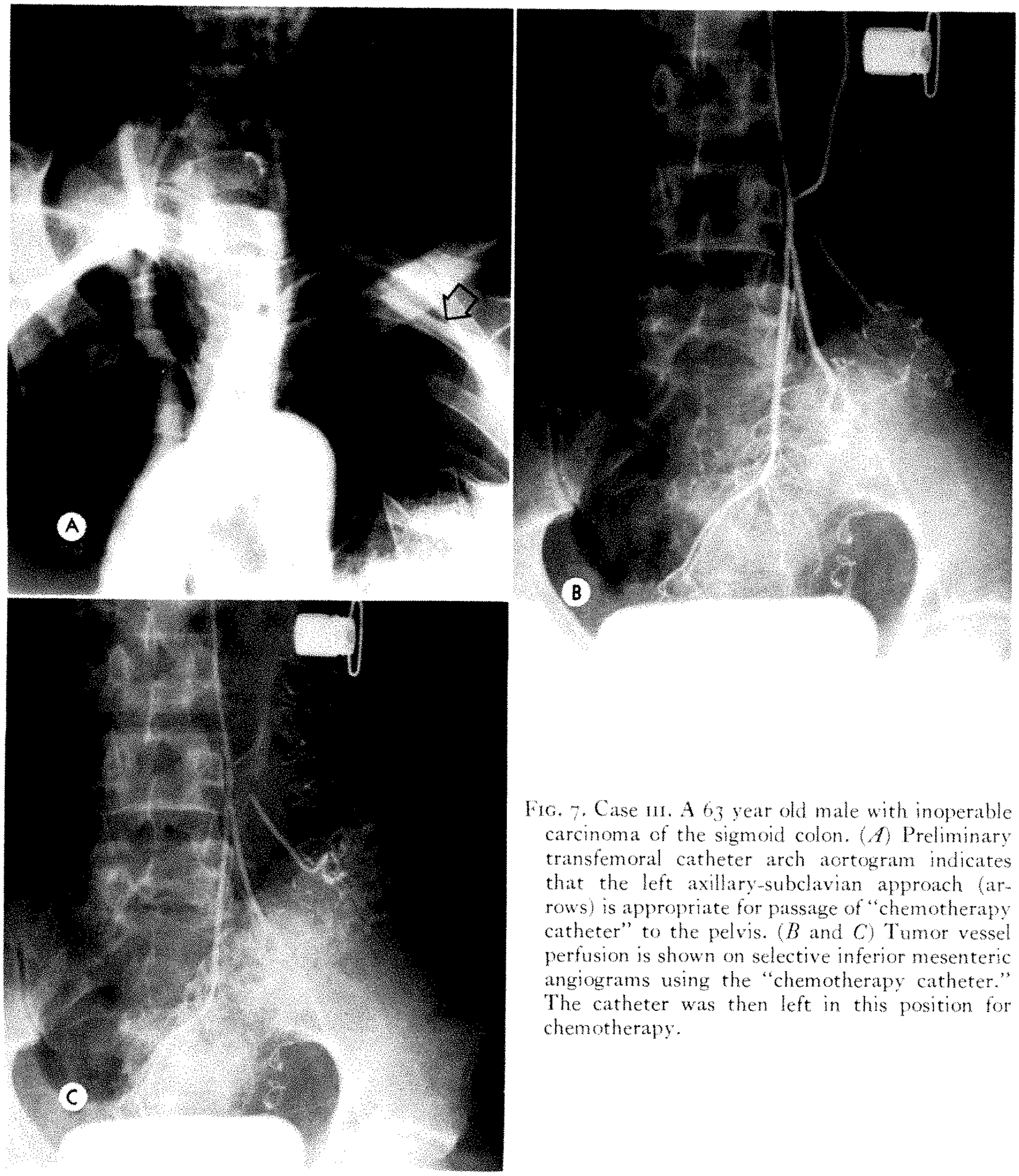

Fig. 7. Case III. A 63 year old male with inoperable carcinoma of the sigmoid colon. (*A*) Preliminary transfemoral catheter arch aortogram indicates that the left axillary-subclavian approach (arrows) is appropriate for passage of "chemotherapy catheter" to the pelvis. (*B* and *C*) Tumor vessel perfusion is shown on selective inferior mesenteric angiograms using the "chemotherapy catheter." The catheter was then left in this position for chemotherapy.

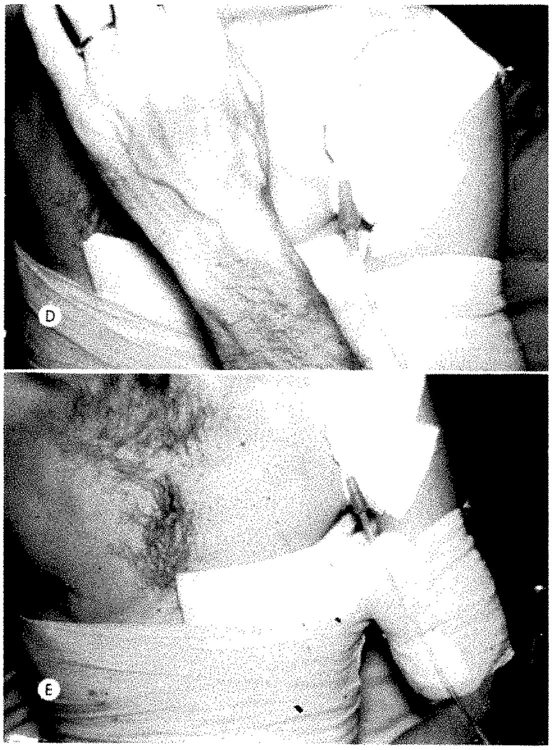

FIG. 7. (*D* and *E*) A padded abduction splint is shown which partially immobilizes the arm and allows comfortable wide range of forearm motion. This catheter was left in place for 16 days with no patient discomfort.

(2) Catheter exploration permits angiographic identification of arterial tumor "feeders" and the disadvantages of tiny catheters, inserted at open surgery, are obviated.
(3) The use of a carotid or axillary catheter insertion site permits comfortable patient ambulation.
(4) Experience gained in this small but continuous series of 12 adult patients would seem to justify further investigation of this approach.

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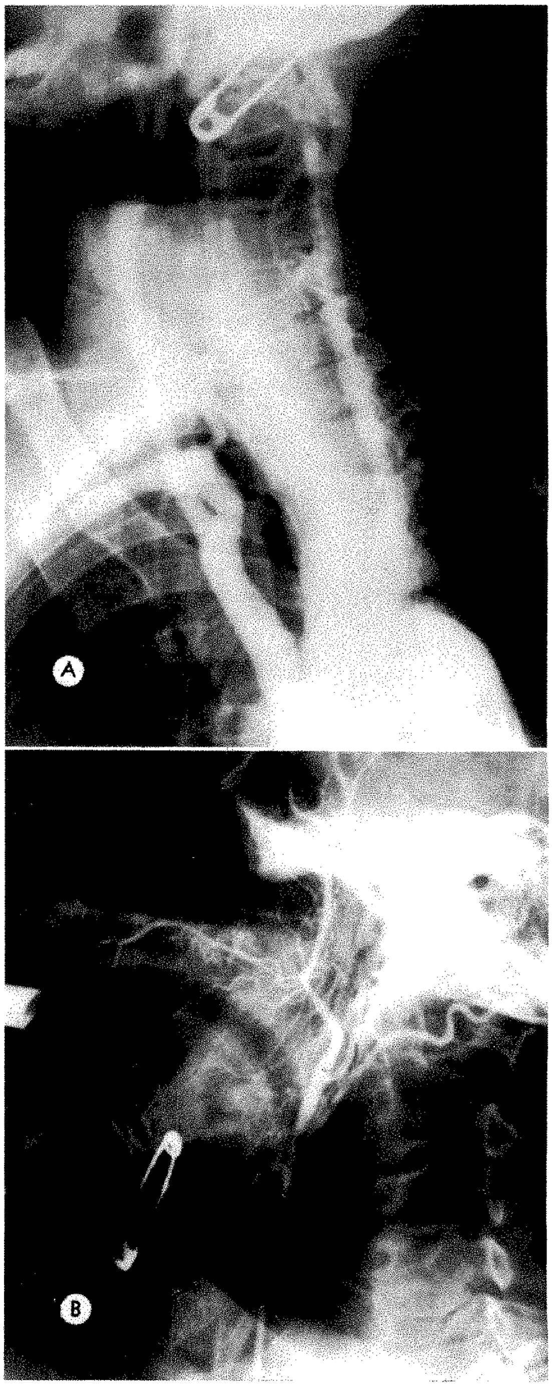

FIG. 8. Case IV. A 78 year old male with extensive squamous cell carcinoma of floor of mouth and submandibular areas, recurrent after radical surgery 1 year previously. (*A*) Transfemoral catheter arch aortography indicates anatomic status of carotid arteries and identifies position of external carotids. (*B*) "Chemotherapy catheter" via left common carotid insertion in left external carotid artery perfuses the tumor areas which are hypovascular. Chemotherapy perfusion was administered through this catheter for a period of 13 days.

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PREOPERATIVE IRRADIATION WITH CYSTECTOMY IN THE MANAGEMENT OF BLADDER CANCER*

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THIS paper deals with certain aspects of a pilot study on the use of preoperative irradiation with cystectomy in the treatment of selected patients with bladder cancer.

ASSESSMENT OF TUMOR

Methods for the assessment of tumor-host relationships with the objective of obtaining reliable indications of prognosis in the individual patient remain elusive.

In this analysis, stage alone has been utilized to characterize the tumor. The Marshall[2] modification of the system described by Jewett and Strong[1] defines 7 stages of bladder carcinoma (Fig. 1). Because of the small number of cases, this system of staging has been simplified into three basic categories (Fig. 2). Justification for this simplification is derived from the observation both in autopsy and clinical studies that "superficial" or "low stage" tumors are associated with regional lymph node metastasis in approximately 5 per cent of cases, whereas "deep" or "high stage" tumors are associated with lymph node metastasis in about 40 per cent of cases. Experience has demonstrated a poor prognosis for patients whose bladder tumors have invaded organs adjacent to the bladder (*e.g.* vagina, prostate, seminal vesicle, uterus), whether or not lymph node metastasis has occurred concurrently: tumors of such extent are accordingly placed in the "metastatic" category along with those in which lymph node or other metastases have been demonstrated.

The preoperative *clinical* estimate of the stage of the tumor derived from careful cystoscopy, bimanual examination and biopsy under anesthesia and from the adjunctive use of intravenous pyelography agrees with the *pathologic* extent of the cancer determined by examination of the cystectomy specimen approximately 80 per cent of the time, relative to whether the tumor is of superficial or deep stage. The greater error is in underestimating rather than in overestimating the extent of the lesion. Analysis of the accuracy of *clinical* staging in predicting *pathologic* extent of the tumor from year to year over the past 15 years does not indicate significant change.

SELECTION OF PATIENTS

Preoperative radiation therapy was planned for all patients in whom cystectomy was recommended excepting those patients referred for cystectomy as radiation therapy failures.

In general, patients were selected for cystectomy for one of the following basic clinical situations: (1) *Multiple low stage carcinomas*, either initially too extensive for conservative treatment, or too rapidly recurrent after conservative treatment for further conservative efforts, or repeatedly recurrent following conservative surgical efforts—particularly if the lesions were of high grade either initially or subsequently; (2) *high stage tumors not suitable for segmental resection*, either by virtue of a history of prior tumor elsewhere in the bladder, or by reason of multiplicity, or by reason of proximity to the bladder neck. In the latter regard, a tumor situated 2 cm. or less from the bladder neck was categorically judged unsuitable for segmental resection.

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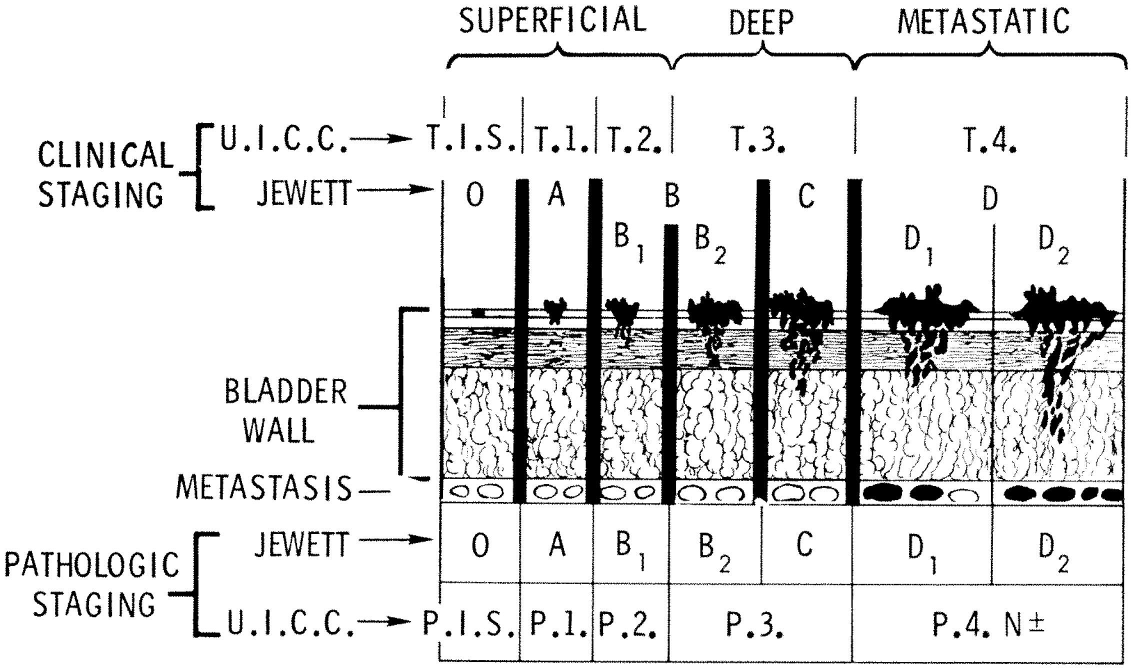

FIG. 1. The seven possible stages of bladder cancer. The clinical and pathologic equivalents of the Jewett and the U. I. C. C. (Unio International is Contra Cancrum) systems of staging are indicated.

METHOD OF TREATMENT

The irradiation plan was to administer 4,000 rads to the bladder and true pelvis by supervoltage in a period of 4 weeks, usually with cobalt 60 teletherapy and usually through anterior and posterior portals measuring 10×10 or 10×12 cm. Other sources of supervoltage radiation and other techniques were occasionally used. Radical cystectomy was usually performed between 1 and 3 months following the completion of radiation therapy. In the male patients, the operation ordinarily included excision of the bladder, prostate and seminal vesicles with enveloping fat and fascia and overlying peritoneum. In the female patient, the usual operation consisted of removal of the bladder, urethra, fallopian tubes, ovaries, uterus and at least the anterior vaginal wall. In both sexes a bilateral pelvic lymph node dissection extending from the midportion of the common iliac arteries distally along the external iliac artery to the inguinal ligament and including the obturator, external iliac, and internal iliac lymph nodes was also performed. All pari-

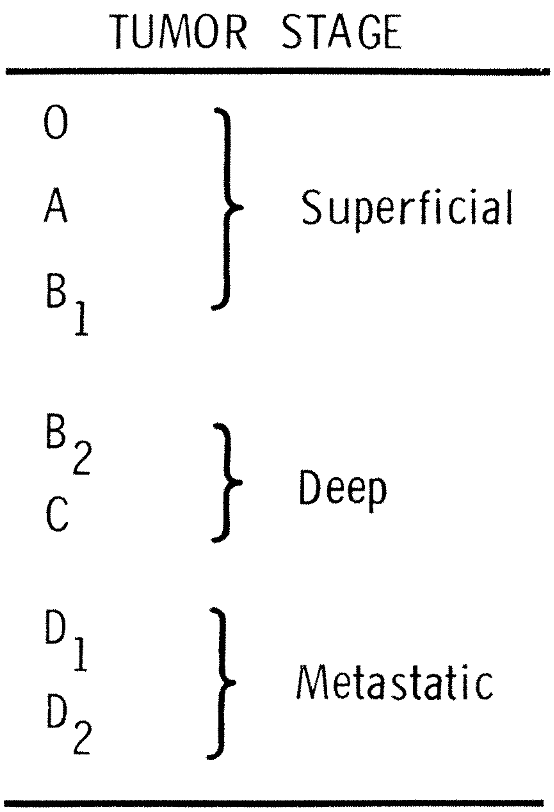

FIG. 2. Simplified staging of bladder cancer.

Table I

BLADDER CANCER
327 PLANNED CYSTECTOMIES
1959–1966

	No. of Cases	No Operation		Resectable		Nonresectable	
No RT	32	2	6%	25	78%	5	16%
Protocol RT	177	39	22%	121	68%	17	10%
Nonprotocol RT	109	8	7%	81	74%	20	18%
Other RT	9	1	11%	8	89%	0	

RT = Radiation Therapy.

etal peritoneum of the true pelvis and much of that of the adjacent false pelvis was removed in continuity with the surgical specimen, making reperitonealization technically impossible. In a few, elderly, poor risk patients, lymph node dissection was either curtailed or omitted entirely but other features of the radical excision were retained.

RESULTS

Experience with this program is briefly reviewed in terms of operative mortality and morbidity, effects of radiation therapy on the tumor, and survival. In an attempt to place these results in perspective, two other series of patients who had radical cystectomy for bladder cancer have been utilized. The validity of the resulting comparisons may be questioned since the three series do not constitute a controlled study and since the series were not simultaneously accumulated, but for the three series it may be stated that: (1) the methods and the accuracy of clinical staging were similar, and, (2) the technique of radical cystectomy was the same. The criteria for selection of patients for cystectomy have been essentially unchanged over the past 15 or more years and, even were criteria changed, categorization of patients according to tumor stage would minimize the influence of other factors of selection on survival, since tumor stage is such a dominant determinant of prognosis in any event.

Between 1959 and 1966, 327 cystectomies were advised in patients with bladder cancer at the Memorial or James Ewing Hospitals (Table 1). In 32 patients (no radiation therapy) preoperative irradiation was not employed for the following reasons: (1) because of patient refusal to submit to irradiation; (2) because economic reasons in patients from foreign countries made a condensed form of treatment imperative; (3) because of the necessary presence of some form of catheter drainage; (4) because of bleeding of sufficient magnitude to make delay for radiation therapy impractical; (5) because of a markedly diminished bladder capacity; or (6) because of rapidly progressing bilateral upper urinary tract obstruction.

In 9 relatively recent patients (other radiation therapy) the protocol course of radiation therapy was arbitrarily not given in favor of an alternative program of preoperative irradiation in which 2,000 rads were delivered to the bladder and true pelvis by supervoltage radiation within a period of 10 days and followed within a period of 2 weeks by cystectomy.

In 109 patients (nonprotocol radiation therapy) protocol irradiation was made impossible by the fact that the patients had had prior radiation therapy, usually 6,000 rads to the bladder and varying portions of the adjacent pelvis by supervoltage, usually over 6 to 8 weeks, and usually from a few months to a year or more prior to cystectomy. These patients, with few exceptions, had had radiation therapy elsewhere and had been referred for further treatment as radiation failures.

TABLE II

OPERATIVE MORTALITY AND MORBIDITY AFTER RADICAL CYSTECTOMY

	Old Series		1959–1966 Series			
			Protocol	RT	Nonprotocol	RT
Deaths	16/145	11%	14/121	12%	12/81	15%
Complications	62/145	43%	52/121	43%	43/81	53%

RT = Radiation Therapy.

In the remaining 177 patients (protocol radiation therapy) protocol irradiation to be followed by radical cystectomy was planned.

In Table I the different groups of cases are tabulated and the nonoperated, resectable, and nonresectable cases in each group indicated. The proportion of resectable and nonresectable cases in each category is grossly similar. A relatively large number of patients having protocol radiation therapy did not come to cystectomy. This was primarily a consequence of symptomatic and objective improvement following radiation therapy with resultant patient refusal or, less commonly, physician reluctance to proceed with cystectomy in the face of such improvement.

To provide some basis for evaluation of the effects of radiation therapy on patients selected for cystectomy, an experience with 230 patients subjected to radical surgery for bladder cancer and previously reported by Whitmore and Marshall[3] was reviewed. In this series, those patients who had either prior radiation therapy or pelvic exenteration or both were excluded, leaving 145 patients who were subjected to radical cystectomy for bladder cancer in whom prior radiation therapy had not been employed. This group of cases is referred to in this anlysis as the "old series." Pertinent comparisons will be made between the "old series," the series receiving protocol radiation therapy, and the series simultaneously treated with the latter group who had received prior "nonprotocol radiation therapy."

The operative mortality and morbidity in the three series are summarized in Table II. No significant differences in either operative mortality or morbidity are apparent. Wound morbidity in the form of prolonged drainage from the vesical space was a sufficiently striking feature in the irradiated series so that the routine drainage of wounds has been abandoned in the past 3 years.

Information relative to the effects of the protocol radiation therapy on the bladder tumor can be derived from a comparison of the preradiation clinical stage of the tumor to the postradiation, and the postsurgical pathologic stage (Table III). This tabula-

TABLE III

COMPARISON OF PRERADIATION CLINICAL STAGE TO POSTSURGICAL PATHOLOGIC STAGE

Clinical Stage		Pathologic Stage				
		No tumor	*In situ*	A, B_1	B_2 C	D
OAB_1	44	6	10	17	4	7
B_2C	79	9	1	15	21	33
D	15			1	5	9
Total	138	15	11	33	30	49

Table IV

SURVIVAL OF PATIENTS HAVING PROTOCOL RADIATION THERAPY ONLY

Clinical Stage		2 Years	3 Years	4 Years	5 Years
OAB_1	(17)	11/16 (69%)	8/15 (53%)	3/8 (38%)	1/5 (20%)
B_2C	(18)	8/16 (50%)	5/15 (33%)	1/13 (8%)	1/8 (12%)
D	(4)	1/3	1/2	1/2	

tion includes 121 patients on whom cystectomy was actually accomplished and an additional 17 patients in whom laparotomy revealed nonresectable neoplasm. Since, in all but two instances, pretreatment biopsies revealed tumor beyond the *in situ* stage and since deliberate efforts to eradicate tumor by transurethral measures prior to radiation therapy were not made, the conclusion seems inescapable that in 26 of the 138 patients (with the two possible exceptions mentioned above), a reduction in tumor stage occurred as a consequence of the irradiation. Multiple blocks were examined from the bladders of these patients but step and serial sections were not routinely employed. Of 15 patients in whom no residual tumor was found at the time of cystectomy 4 have died, but autopsies in 2 of the latter revealed no evidence of cancer and there was no clinical evidence of cancer in the other two. The remaining 11 patients are alive and apparently well: 6 less than 2 years, 1 each for 2, 3 and 4 years, and 2 for 5 years or more. Of 11 patients with *in situ* cancer only in the cystectomy specimen, 2 have died of bladder cancer and 1 of an unrelated cause. Of the surviving 8 patients, 6 have survived for more than 2 years including 2 for 3 years, 1 for 4 years, and 1 for more than 5 years.

Survival data for the 39 patients who had protocol radiation therapy and who did not have subsequent laparotomy or cystectomy are shown in Table IV. In this group there were 11 patients (7 clinically superficial and 4 clinically deep) whose biopsies and urinary cytologic studies became negative following radiation therapy and 5 have died, 3 from cardiovascular causes and 2 from cancer, although whether the cancer death was of thyroid or bladder origin is uncertain in 1 case. Of the remaining 6 patients, 1 is living less than 2 years, 1 for 2 years, 3 for 3 years, and 1 for 5 years from the date of radiation therapy.

In Table V survival rates for patients with *clinically* superficial lesions from each of the series are calculated at 2, 3, 4, and 5 years on the basis of the number of survivors relative to the total number at risk for the respective follow-up interval. Only resectable cases (Res.) are included in the "old series." For the two radiation series, two analyses have been included: that which is designated "All" includes all the

Table V

SURVIVAL RATES FOR DIFFERENT SERIES

CLINICAL STAGES: OAB_1

		2 Years	3 Years	4 Years	5 Years
Old Series (Res.)	(51)	33/51 (65%)	28/51 (55%)	23/51 (45%)	22/51 (43%)
All Protocol RT	(61)	35/49 (71%)	26/44 (59%)	12/29 (41%)	6/19 (32%)
Res. Protocol RT	(44)	24/33 (73%)	17/28 (61%)	9/21 (43%)	5/14 (36%)
All Nonprotocol RT	(36)	17/30 (57%)	8/22 (36%)	7/18 (39%)	4/10 (40%)
Res. Nonprotocol RT	(30%)	15/25 (60%)	6/17 (35%)	5/13 (38%)	3/8 (38%)

RT = Radiation Therapy. Res. = Resectable.

Table VI

SURVIVAL RATES FOR DIFFERENT SERIES
PATHOLOGIC STAGES: OAB_1

		2 Years	3 Years	4 Years	5 Years
Old Series	(51)	37/51 (73%)	33/51 (65%)	29/51 (57%)	28/51 (55%)
Res. Protocol RT	(59)	31/43 (72%)	22/34 (65%)	13/25 (52%)	7/17 (41%)
Res. Nonprotocol RT	(35)	18/26 (69%)	10/21 (48%)	7/18 (39%)	4/12 (33%)

RT = Radiation Therapy. Res. = Resectable.

Table VII

SURVIVAL RATES FOR DIFFERENT SERIES
CLINICAL STAGES: B_2C

		2 Years	3 Years	4 Years	5 Years
Old Series	(89)	27/89 (30%)	21/89 (24%)	20/89 (22%)	18/89 (20%)
All Protocol RT	(97)	32/82 (39%)	19/66 (20%)	18/56 (32%)	8/39 (20%)
Res. Protocol RT	(65)	21/52 (40%)	14/40 (35%)	12/34 (35%)	7/23 (30%)
All Nonprotocol RT	(48)	13/34 (38%)	8/27 (30%)	4/19 (21%)	3/10 (30%)
Res. Nonprotocol RT	(40)	12/26 (46%)	8/23 (35%)	4/16 (25%)	3/9 (33%)

RT = Radiation Therapy. Res. = Resectable.

patients appropriately staged clinically (OAB_1), whether or not cystectomy was attempted; and that which is designated "Res." includes only those patients in whom cystectomy was actually accomplished. The 5 year survival rates in these different groups ranged from 31 to 43 per cent, and indicate no substantial differences.

In Table VI a similar tabulation is given for the three series on the basis of the *pathologic* staging of the surgical specimen for patients in whom cystectomy was accomplished (Res.). Although the number of cases in each series is small, the 55 per cent 5 year survival rate obtained in the "old series" is better than the 41 per cent attained in the protocol series or the 33 per cent attained in the nonprotocol series. However, at 2, 3 and 4 years the survival rates in the "old series" and in the protocol series are quite similar and this fact coupled with a relatively large number of deaths from noncancer causes between the 4th and 5th years in the protocol series can account for the relatively poor 5 year results in the protocol series. Furthermore, a reduction in tumor stage as a consequence of preoperative radiation therapy could result in the inclusion of patients in the pathologic low stage category whose lesions were initially of high stage, possibly contributing to

Table VIII

SURVIVAL RATES FOR DIFFERENT SERIES
PATHOLOGIC STAGES: B_2C

		2 Years	3 Years	4 Years	5 Years
Old Series	(60)	17/60 (28%)	12/60 (20%)	11/60 (18%)	10/60 (17%)
Res. Protocol RT	(30)	12/26 (46%)	8/22 (36%)	6/15 (40%)	3/8 (38%)
Res. Nonprotocol RT	(16)	5/10 (50%)	3/8 (38%)	2/6 (33%)	2/2

RT = Radiation Therapy. Res. = Resectable.

Table IX

SURVIVAL RATES FOR DIFFERENT SERIES
PATHOLOGIC STAGE: D_1

		2 Years	3 Years	4 Years	5 Years
Old Series	(34)	9/34 (26%)	5/34 (15%)	3/34 (9%)	2/34 (6%)
Protocol RT	(32)	4/26 (15%)	1/18 (6%)	0/15	0/13
Nonprotocol RT	(30)	5/22 (23%)	1/15 (7%)	0/10	0/4

RT = Radiation Therapy.

poorer survival rates in the protocol series.

Table VII indicates survival rates for patients with *clinically* high stage lesions from each of the three series. Five year survival rates ranged from 20 per cent to 33 per cent and demonstrate no remarkable differences.

In Table VIII a similar tabulation is given for the three series on the basis of the *pathologic* staging of the surgical specimen in patients in whom cystectomy was accomplished. The survival rates at 2, 3, 4 and 5 years are all better in those patients having protocol radiation therapy than in the "old series."

For patients with tumors in the metastatic stage category the survival outlook following cystectomy is poor, and, at best, has not been helped by prior radiation therapy (Table IX).

DISCUSSION AND CONCLUSION

The number of patients involved in these studies is small. The precise comparability of the patients in the three series can be questioned, although the overwhelming significance of tumor stage in determining prognosis is well established by past radiation therapy and surgical therapy experiences. At the worst, radiation therapy has not added prohibitively either to mortality or morbidity following cystectomy. Radiation therapy has produced an unequivocal destruction of tumor in slightly more than 10 per cent of the cases treated according to the protocol and a reduction in tumor stage in at least another 6 to 7 per cent of cases. The survival of patients with low stage tumors following cystectomy has not been appreciably altered by the addition of preoperative radiation therapy but in patients with high stage tumors an improvement in survival is suggested. Whether this improvement is a consequence of the radiation therapy is debatable, but the tumor disappearance or the reduction in tumor stage seen in some patients after preoperative radiation therapy lends evidence to such a possibility.

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PREOPERATIVE IRRADIATION FOR CARCINOMA OF THE BLADDER*

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DESPITE advances in the application of surgery and irradiation the treatment of bladder carcinoma remains unsatisfactory. Five year survival rates following radiation therapy approximate 20 per cent for all patients seen in a large radiotherapy department,[2,8] and 28 per cent for those with invasion of muscle or perivesical tissue. Similar rates have been achieved by surgery in a selected population suitable for operation.[1] With either method, treatment failure is due to locally recurrent pelvic disease in the majority of patients.[8,11]

Improved tumor control rates in animal systems subjected to preoperative irradiation suggested the use of this technique in the treatment of bladder cancer.[3,4] We wish to present the philosophy and early results of such a program carried out at the Presbyterian Hospital of the Columbia-Presbyterian Medical Center.

Preoperative radiotherapy programs range in purpose from devitalization of cells and alteration of the tumor bed to sterilization of tumor which may not be removed at operation. The first purpose can be achieved with a low-moderate radiation dose, but the latter requires doses of the order of 5,000–7,000 rads. Our experience and that of others showed increased morbidity and operative difficulty following a full course of radiotherapy. Therefore, a program of moderate dose irradiation, 3,000 rads in 3 weeks, was designed to augment the basic surgical attack without interfering with its accomplishment.[7] The guiding surgical philosophy was to preserve bladder function, treating by endoscopic resection and avoiding cystectomy whenever clinically feasible.

MATERIAL AND METHOD

Fifty-one patients were registered in a prospective, noncontrolled study from May, 1960 through April, 1966. Private and service patients were included, but not all eligible patients in either category were referred for study.

The age and sex distribution is shown in Table I. There were 33 males and 18 females with a mean and median age between 60 and 65 years. Hematuria was present in 43 patients. The histologic diagnosis was transitional cell epithelioma in 41, anaplastic carcinoma in 2, and squamous cell epithelioma in 8. In 6 of the 41 patients with transitional cell epithelioma, squamous metaplasia was also described.

The program under study is outlined in Table II. Following initial evaluation, clinical staging was carried out according to

Table I

AGE AND SEX INCIDENCE

Years	Male	Female	Total
40–44	1	1	2
45–49	3	0	3
50–54	1	0	1
55–59	8	5	13
60–64	5	4	9
65–69	4	2	6
70–74	7	6	13
75–80	4	0	4
Total	33	18	51

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Table II

TREATMENT PROGRAM

1. Evaluation
2. Staging
3. Irradiation—3,000 rads in 3 weeks
   Anterior—Posterior ports, 12 cm.×12 cm.
   Cobalt 60 teletherapy or 22.5 mev. betatron
4. Re-evaluation—3–6 weeks later
5. Surgery—Endoscopic resection
   Partial cystectomy
   Total cystectomy
   Radical cystectomy+lymph node dissection
   (Irradiation to 6,000 rads)

the Marshall modification[5] of the system of Jewett and Strong. A preoperative course of 3,000 rads tumor dose to the true pelvis was then delivered in the majority of cases (45) in 17–23 elapsed days. A tumor dose of 3,500 rads was reached in 2 patients, and 4,000 rads in 4 patients. Supervoltage equipment (Co^{60}, 22.5 mev. betatron) was utilized with conventional fractionation (5 day/week).

Re-evaluation was usually undertaken in 3 to 4 weeks (range 2 days to 15 months) following the last irradiation, depending on the clinical state and cooperation of the patient. When possible, endoscopic resection or partial cystectomy was carried out. When cystectomy was necessary, ureterosigmoidostomy or, more recently, an ileal conduit was established. In 2 patients in whom no tumor was found at cystoscopy and biopsy, additional radiotherapy was given to a total tumor dose of 6,000 rads in "split-course" fashion.

All 51 patients completed the planned course of radiotherapy. Bowel and bladder reactions were usually absent to mild in degree; in only an occasional case was it necessary to reduce the daily dose.

Surgery was undertaken in 41 patients. Only endoscopic resection was required in 4 and in 9 a partial cystectomy could be performed. Cystectomy was required for 21 patients. An unresectable lesion was found in 7.

Survival data according to stage are shown in Table III. Only patients with currently demonstrable disease or proven recurrence at demise are classified as "with disease." Fifty-three per cent (8/15) of Stage A patients remain alive, but 1 required additional therapy. In Stage B, only 32 per cent (8/25) of patients are alive; 3 of these 8 survivors are failures of the protocol and required additional treatment. There are no survivors in Stage C (0/9) or Stage D (0/2) patients. If we consider only those patients in whom surgery was undertaken, the salvage rates are: 7/12 (58 per cent)—Stage A; 8/19 (42 per cent)—Stage B; 0/8—Stage C; and 0/2—Stage D.

Ten patients did not have an operation; only 1 remains alive. Nine have died, 4 with proven recurrence; the pelvic status was unknown when 4 others died, 1 with distant metastases, 1 of a second primary cancer of the colon, and 2 having refused further treatment. One man refused operation, received 6,200 rads in split course fashion with a 2 month rest after the first 3,200 rads, and died of intercurrent disease with a negative bladder at postmortem examination 16 months later.

DISCUSSION

The basic goal of improving survival rates while preserving bladder function led to the establishment of a preoperative radiotherapy program which would be well tolerated and would not interfere with surgery. Cystectomy was avoided when possible. Toward this end, each patient was carefully restudied with cystoscopy and biopsy after irradiation. From the clinical and histologic data we hoped to establish criteria to guide us in the choice of treatment (radical operation *vs.* conservative operation, radiotherapy) and to resolve doubts concerning the clinical course of disease during the interval before operation.

CONCLUSIONS

1. The approximately 6 week delay between onset of irradiation and operation

TABLE III

SURVIVAL—MONTHS*

Stage A

	Alive 8 Without Disease 8	Dead 7	
		Without Disease 5	With Disease 2
12 Operated	33, 32[a], 25, 25[b], 23, 17, 14, 15[f]	31[f], 14[f], 5	21, 3
3 Not Operated		20, 16	

Alive/at Risk = 8/15 (53 per cent).

Stage B

	Alive 8 Without Disease 8	Dead 17	
		Without Disease 3	With Disease 14
19 Operated	44, 36[f], 34, 22[f], 22, 19[f], 16, 15	23[f,m]	36, 26, 23, 14, 12, 9, 8, 7, 7, 7
6 Not Operated		1[a], 8[f,s]	45, 10, 6, 1

Alive/at Risk = 8/25 (32 per cent).

Stage C

	Alive 0 Without Disease	Dead 9	
		Without Disease 5	With Disease 4
8 Operated		7[s], 6[s], 4[s], 4[s], 2[s]	7, 7, 6
1 Not Operated		16[m]	

Alive/at Risk = 0/9.

Stage D

	Alive 0 Without Disease	Dead 2	
		Without Disease	With Disease 2
2 Operated			12, 5
0 Not Operated			

Alive/at Risk = 0/2.

* Only patients with current demonstrable disease, or proven recurrence at demise, are classified as "with disease." All others are classified as "without disease" despite documented recurrence if further treatment appears to have controlled the process.

[a] = Lost to follow-up. [b] = Lung metastasis, excised. [f] = Protocol failure, additional treatment given. [m] = Postmortem study, 6,000 rads. [s] = Postoperative death.

is not deleterious. In no patient did the findings at cystoscopy with bimanual pelvic examination progress so that operation was precluded.

2. Surgery was not more difficult after 3,000 rads except for increased adherence of lymphatics and perivascular tissue along the iliac vessels.

3. Three thousand rads is too low a dose to achieve local tumor control. Persistent

disease was demonstrated at re-evaluation in 43/49 cases (88 per cent); 2 patients refused further study or treatment. In only 6 could no tumor be found.

4. Histologic examination after 3,000 rads is a hazardous base upon which to plan treatment. Of the 6 patients with a "negative" histologic evaluation, 4 died with proven local recurrence, 1 died of distant metastases without a statement concerning pelvic disease, and 1 remains alive at 34 months after radical cystectomy. In another 2 patients, the response to 3,000 rads was so good that the dose was carried to 6,000 rads in 9 weeks in "split course" fashion in lieu of surgery; both suffered recurrence in less than 1 year. To complicate the picture still further, 1 patient underwent cystectomy when tumor was seen in the re-evaluation biopsy, but no tumor was found in the bladder specimen. Similar difficulty has attended the evaluation of histologic studies following irradiation with doses of 4,000–7,000 rads.[9]

5. Conservative surgery alone following moderate dose irradiation for invasive carcinoma is not likely to improve long-term survival rates. The short-term results presented are no better than the results of irradiation alone or surgery alone.[1,2,8]

The goal of improving survival results while preserving bladder function remains elusive. The concept of invasive bladder cancer being a disease of the entire bladder urothelium, and the possibility of subclinical circumferential tumor spread in the bladder wall serve to explain the failure of this conservative approach.[6] In the future evaluation of combined treatment for invasive carcinoma we plan to rely on cystectomy while gradually raising the preoperative irradiation dose.

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CANCER OF THE BLADDER*

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THERE are three aspects of urothelial tumors of contemporary interest. The first is the initiation of tumors due to the exposure of workmen to an environment containing carcinogenic substances. The second is the problem of multifocal urothelial disease, whether it be due to implantation of exfoliated cells, the presence of carcinogens in the urine, or other factors. The third is the problem of infiltration which may be iatrogenic due to bad surgery, possibly due to a chromosomal abnormality, but which is of bad prognostic significance.

INITIATION OF INDUSTRIAL ORIGIN

Rehn in 1895 suggested that workmen involved in the processes of manufacture of aniline in a dye factory developed tumors in their bladder as the result of exposure to aniline. This original observation (but unfortunate concept) of an "aniline dye tumor" crept into clinical use and the idea that aniline was the sole causative factor acted as a screen to delay the search for the real carcinogenic agent. Hueper in 1938 showed that β-naphthylamine, the intermediate compound in the preparation of dyes, was carcinogenic to dogs, and at this time suspicion was aroused that tumors occurring in men employed in various industries could be the result of exposure to industrial chemicals. Events during the next few years prevented further research, but in 1949 the Imperial Chemical Industry voluntarily ceased manufacture of β-naphthylamine in England and withdrew all known stocks of this chemical. During the last two years the manufacture of benzidine and of α-naphthylamine have also been stopped in England, but not in America.[6]

All these compounds are not equally dangerous, nor are the trade processes; for example, those men who were employed in the distillation of β-naphthylamine have developed bladder tumors in every case, but men exposed to benzidine had a relatively smaller risk, although it still represents something like twenty times the risk of the normal population.[1] In any factory certain men are considered to be higher risks than others; for example, men working in the mixing room weighing out the raw β-naphthylamine, men working in the rubber mill where the raw rubber was processed, and men working with steam presses where the hot vapors were given off as the press opened, are all considered to be high risk workers. Men working on the factory floor in less intimate contact with the chemicals were considered medium risk, but anybody working within the factory, whether he be managing director or the porter at the gate, was considered to be at risk if there was any question of exposure at any time to industrial chemicals.

In England legislation has been introduced which entitles these men to a pension if they have been exposed to these chemicals. But more important than compensation is the fact that once a risk has been recognized steps can be taken to withdraw the dangerous substance and at the same time screening procedures can be introduced to detect the development of any early neoplastic lesions in the workmen who have been exposed.

The importance of chemical carcinogenesis to the practicing clinician, whether he be a surgeon or a radiotherapist, is twofold. Firstly, by the recognition of the industrial risk the process can be stopped,

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screening can be introduced, and compensation awarded. But in addition to these factors there is a second aspect, the stimulus given to research into etiologic agents in the evolution of urothelial tumors and the possible role of urogenous endogenous carcinogens.

The recognition of risk. By 1954 the Association of British Chemical Manufacturers had conducted a survey of workmen exposed to industrial chemicals. By chance the records of the Birmingham Cancer Registry were used as a control and this revealed to everybody's surprise, that the rubber industry had an exceptionally high incidence of bladder tumors, and that this industry had been one of the largest users of β-naphthylamine. Since 1957, the rubber industry, acknowledging the past risk, has screened a proportion of the workers exposed to these chemicals. *Routine cytologic screening, (which was not done selectively according to risk) has resulted in 63 asymptomatic tumors being detected in 80,000 examinations of urine.* Furthermore, there have been smears apparently positive where no tumor has yet been recognized cystoscopically, and many other nonmalignant lesions have been detected as a result of this routine screening.

In 1965 the cable industry, which also used hot rubber, compounded with β-naphthylamine, was suspected; there is now overwhelming evidence that in this industry among the men who handled the β-naphthylamine powder, who worked in the rubber mill, or who handled the hot extruded rubber, there is a very real risk of developing a bladder tumor, on average 18 years after the initial exposure.[3]

Other industries and occupations, where the risk has been recognized, include the retort workers in gas works, where naphthylamine has been detected in the atmosphere of the retort house, and rat catchers, who at one time used α-naphthylamine extensively as a rat poison both in England and in America.

Compensation. When the diagnosis has been established that a worker has a tumor of the urothelium, compensation is awarded provided that the worker can prove that he was exposed to a specified group of chemicals, including benzidine, after 1948. If, however, the worker could prove that, after the dangers were known, he was still exposed to these chemicals then he could well sue for negligence. A further point is whether the employers are also liable for negligence if having admitted the carcinogenic risk they have failed to provide cytologic screening of the men at risk.

This group of workers represent only a small portion of the total incidence of urothelial disease, but in our series, the men whom we have established as having developed their disease as a result of industrial exposure, represent 3 per cent of our total clinical material.

This figure is a minimal one since there may be other patients in whom we have failed to elicit an industrial history but it is a group that could have been prevented. In those countries where there is no control of these chemicals, the group of men with, or about to develop, urothelial tumors, is still increasing.

The responsibility rests with the clinician to identify any industrial risks that could have had an etiologic role in the initiation of urothelial tumors, but once this has been identified the responsibility for removing the risk and paying compensation rests with the government of the country concerned.

IMPLANTATION OR MULTIFOCAL ORIGIN

The controversy between those clinicians who supported the implantation theory (Albarran in 1903) and those who supported the idea of multifocal origin (Hansemann in 1890) has raged for three quarters of a century, but it must be realized that these theories are not mutually exclusive nor may they be the only explanations of the clinical facts.

Although it may well be true that exfoliated cells can implant, especially on the traumatized mucosa, there is little factual, as opposed to circumstantial evi-

dence to support this view. McDonald and Lund[7] implanted tumors in the non-functioning pouch of a dog's bladder, but others have based their conclusions on the time sequence—that ureteric tumors precede tumors in the bladder, or that bilateral tumors are rare, or that removal of a kidney and ureter containing tumor will arrest the disease.

With improved methods of treatment and the appreciation that multiple tumors are common, evidence is accumulating to suggest that a bladder lesion may be a solitary manifestation of neoplasia but is more likely, when taken over a period of years, to be the first manifestation of neoplasia of the whole of the urinary tract.

In reviewing our material over the last 15 years the most striking finding is the high incidence of multiple lesions when there has been a long survival period for follow-up.

All our patients who have had a nephroureterectomy and have been followed-up have developed lesions in their bladders, but in some there has been an interval of 14 years before the bladder lesion was recognized.

Nine patients who were under treatment by cystoscopic methods have, during the follow-up period, developed lesions in a previously normal upper tract. In one of these the precipitating factor appeared to be stasis in a hydroureter following fibrosis (but not infiltration) of the intermural ureter—a clinical observation confirming the work of Scott and Boyd.[9]

Four patients, following cystectomy and ureteric diversion, have developed lesions of one kidney and ureter. One of these, a man who has had a nephroureterectomy, cystectomy and urethrectomy, continues to excrete neoplastic cells from his remaining kidney.

In our cystectomy series, where the ureters are now examined routinely, there has been found to be a 10 per cent incidence of either *in situ* or frankly proliferative carcinomatous lesions within the last 4 inches of the ureter.

The number of patients reported in the literature with bilateral asynchronous or synchronous lesions of both upper tracts is relatively small and some are due to industrial exposure. However, with more frequent radiologic studies we have seen 4 patients, none of whom had been exposed to industrial chemicals, treated in our clinic for bilateral lesions, 2 more have been discovered at routine postmortem examination, and 3 more were shown to me by colleagues. In 4 of these 9 patients there had never been a lesion in the bladder. To postulate implantation is to impose on credulity.

The results of total cystoprostatectomy in recent years have shown that 12 per cent died from, or developed, a lesion at the triangular ligament in the perineum or in the urethra, especially when the original bladder lesion was a multifocal one, or when there was tumor in the posterior urethra.

Although some of these recurrences could be due to accidental spillage when the urethra was cut at the prostatic apex, many were due to incomplete excision of neoplastic urothelium lining the urethra. Recent work has shown that in 20 per cent of urethras, where there has been a preceding bladder or kidney pelvis lesion, there is evidence of carcinoma *in situ* of the epithelium or in the urethral glands.[4] The modern operation, in all cases of multiple lesions (and mandatory when there are lesions of the posterior urethra), is the one stage, monobloc, cystourethrectomy.

Recently yet another example of the widespread nature of the urothelial disease has begun to be clearly recognized—the spread of transitional neoplastic epithelium along the prostatic ducts and into the prostatic acini. This lesion is a purely surface manifestation and the prognosis appears to be much better than when there has been direct infiltration of the prostate through the bladder base.

In brief, the urothelial disease is a form of neoplasia that is widespread and may involve any part of the urinary tract that is

exposed to urine. Whether these changes are due exclusively to implantation or to exposure to carcinogens, or whether lymphatic spread, as suggested by Connelly,[2] or a virus, may also play a part, remains to be proved. The too facile acceptance of one theory to the exclusion of all others may well delay the true understanding of the nature of this disease.

INFILTRATION

When infiltration can be recognized clinically, the disease is nearing the terminal phase. Every effort must be made to prevent infiltration.

At the onset, neoplasia starts as an intraepithelial cytologic change, exfoliated cells may be present in the urine and there may be an irritative but not an infected cystitis. A sterile cystitis with little if any change to be seen cystoscopically frequently indicates the early stages of mucosal carcinomatosis.

As the disease progresses symptoms, usually bleeding, may appear, but symptoms are often delayed for many years after the urothelial change has been detected by Papanicolaou smears.

The stage of mucosal proliferation is variable, it may persist for many years without showing any evidence of infiltration, or infiltration may commence early and proceed rapidly without intervention.

The natural history of the disease does not include fungation through the abdominal wall. When this occurs, it is due to ill judged surgery opening up tissue planes and implanting cells or clumps of cells on the surface of the wound. With care and proper selection of patients this complication of open bladder surgery can be avoided (R.M.H. series 1.8 per cent), but when it does occur it is iatrogenic in origin, and not due to the natural behavior of the tumor. Although this complication is well recognized in open bladder surgery it can also occur with incomplete transurethral excisions where a raw area is left in contact with a partially removed noninfiltrating tumor. When this occurs the tumor is said to have "become malignant." Would any surgeon expect a good result with partial excision of a melanoma or a breast tumor?

Iatrogenic infiltration is not the only explanation since Lamb[6] has been able to show that there is a difference in the chromosomal counts—tumors with a normal chromosomal number whatever the degree of anaplasia rarely show infiltration, whereas tumors with a tetraploid or a variable number of chromosomes nearly always show infiltration. The development of a clone of cells with an abnormal chromosomal pattern may well be the earliest stage of infiltration. Care must be taken to avoid any stimulus liable to produce chromosomal changes.[8]

THE CLINICAL PROBLEM OF INFILTRATION

The results of surgery or irradiation when used alone as the sole therapeutic discipline are disappointing. In a series of 104 patients with tumors staged T3, 96 were dead at the third anniversary when treated by supervoltage therapy alone. The results of surgery are little better.

In an attempt to improve the results various combinations of radiotherapy and surgery have been tried.

Before, however, describing these results one must examine the validity of the classification. We use the International Union Staging because, unlike the Jewett-Marshall classification, it is based on a clinical examination but must include biopsy proof of malignancy. We do not believe that it is possible to judge the half way of the bladder muscle clinically since the bladder wall varies in thickness with the degree of distention and the amount of hypertrophy, although with an operative specimen it is possible to differentiate between B1 and B2 reasonably accurately. Nor can we detect clinically or radiologically involvement of lymph nodes within the pelvis (D1) or lymph nodes in the para-aortic region (D2). The Jewett-Marshall classification, being essentially an operative classification, does not have a category for a tumor that is fixed to the pelvic wall, since D1 by definition means

involvement of lymph nodes within the pelvis, not pelvic fixation.

When a comparison is made between the U.I.C.C. clinical and the U.I.C.C. pathologic classification, the major error is in understaging tumors which clinically are called superficial muscle but in fact turn out to be "deep muscle." This error may be due to previous operations, inadequate relaxation, or a biopsy which fails to include bladder muscle. In the deeply infiltrating tumors, however, the accuracy of staging is very exact. There has been no tendency to overstage in this group.

Reverting to the clinical problem of the T3 tumors, the surgery of salvage—*i.e.*, delaying operation after 6,000 r or more, until a recurrent tumor was identified—gave disappointing results. Of 37 patients so treated 8 died postoperatively. There were 21 patients with still deeply infiltrating but lymph node free carcinoma; however, of these only 2 survived 3 years.

A second group of 19 patients was submitted to 4,000–5,000 r irradiation and had a cystectomy within 3 months of treatment. There were 2 operative deaths and 9 survivors.

We believe that a tumor which is deeply infiltrating could respond in one of four ways, either:

1. by *complete regression* potential cure;
2. by *incomplete regression* through a phase of quiescence when surgery could be undertaken with best chance of success
3. by *restraint* when there may be a temporary cessation of growth; or by
4. complete *resistance* when there is no reaction at all.

We have initiated a clinical trial of patients under 70 years of age, fit for radiotherapy or surgery, with deeply infiltrating lesions, and have randomized them into two groups:

(a) where 6,000 r is given and no further treatment; and
(b) where 4,000 r is given and a radical cystectomy carried out a month later.

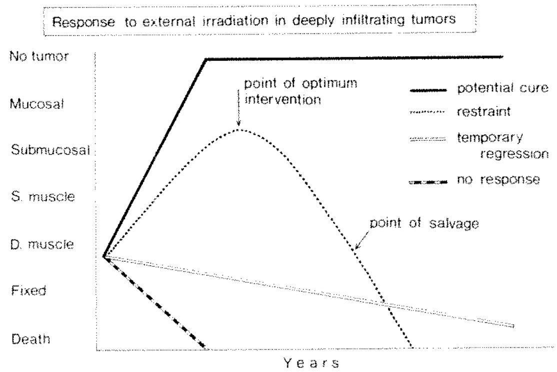

FIG. 1. Response to external irradiation in deeply infiltrating tumors.

Since the trial is in progress no final conclusions can be drawn. Suffice it to say that of 12 patients treated to 4,000 r with histologically proven deeply infiltrating tumors, 2 were found to be tumor free at subsequent cystectomy, and 5 were at a stage which histologically was less than at the first assessment. Five showed no alteration, and positive lymph nodes were found in only one of the series. Although these results are too small and too early for any conclusions to be drawn, they do support the policy that preoperative irradiation to a dose of 4,000 r will help subsequent surgery without increasing mortality or morbidity. More controlled clinical trials from other centers will be needed to confirm or refute our eventual conclusions.

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PREOPERATIVE IRRADIATION IN RECTAL CANCER: INITIAL COMPARISON OF CLINICAL TOLERANCE, SURGICAL AND PATHOLOGIC FINDINGS*

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THE radical surgical treatment for potentially curable rectal carcinoma continues to produce relatively modest long-term survival results. Gilbertsen[9] points out that although improvement in general medical care, anesthesia, and surgical techniques have significantly altered the survival, the gain has been a modest 10 per cent when the series of 1940–1950 are compared to 1951–1959. Morson and Bussey[13] more recently in their review of 1,596 cases, conclude that "surgery alone has little more to offer in the treatment of rectal cancer . . . in spite of all attempts at earlier diagnosis, there has been no significant change in the incidence of the different stages of rectal cancer over the past 25 years." A greater improvement in survival might be mediated through some conceptual change in management.

Good radiobiologic evidence has led to interest in preoperative irradiation as a method with the potential to improve survival even in lesions which in the past had been considered primarily surgical problems. One can expect small groups of cells to be more readily destroyed by radiation therapy than large masses because the former are relatively well oxygenated and, therefore, relatively radiosensitive. Also, it has been shown, both in the laboratory and in human experience, that smaller tumors containing fewer cells are more readily destroyed than larger masses.

Stearns and co-workers,[17] Ruff and co-workers,[15] and Fletcher and associates[7] have used preoperative irradiation either with orthovoltage or supervoltage roentgen rays. Stearns, Deddish and Quan[17] believed that there was significant improvement in survival in those patients given preoperative irradiation who were subsequently classified as Dukes C,[4,5] those in whom regional lymph nodes showed histologic evidence of tumor. In none of these reported studies had randomized controls been used. Furthermore, in the reported works the volume of tissue treated was variable and in none was the treatment plan such as to purposefully include regional lymph nodes.

The present report describes our pilot study in the use of preoperative irradiation in rectal cancer treated to include the primary tumor and regional lymph nodes in the true pelvis and those in the region of the bifurcation of the aorta. Nineteen patients have so far been assigned to a protocol, of whom 10 are in the group receiving preoperative irradiation. However, preliminary to the starting of the randomized series, an additional 9 cases received preoperative irradiation during that time when our group was satisfying itself that a significant dose level could be reached and the operation successfully concluded. We would, therefore, like to set forth our experience related to the 19 patients who received preoperative irradiation before and since the institution of the protocol so that the clinical course of the patients during irradiation, the ability of the surgeon to perform his procedure, the condition of the tissue at operation, and the distribution of gross and microscopic disease could be revealed. The pathologic findings in

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those 9 protocol patients who have been randomized into the surgery alone group are also presented. Details of the anatomic findings in all patients will be amplified in a subsequent report.[19]

PROTOCOL FOR PREOPERATIVE IRRADIATION

Clinically operable patients with rectal carcinoma who have not had a previous malignant tumor are strictly randomized into two groups: preoperative irradiation followed by operation, *vs.* operation alone. The aim of the protocol is to test the possible improvement in surgical treatment of carcinoma of the rectum and rectosigmoid by the use of preoperative irradiation. To be admitted to the protocol, the patient must present with biopsy-proven adenocarcinoma of the rectum. The surgeon must feel that there is a reasonable expectation of resection, and the patient must accept the operation. Other bowel lesions are excluded by barium enema examination, and there must be no evidence of distant disease as revealed by roentgenographic study. The absence of liver metastases is tested by standard liver function studies including bromsulphalein retention and a radioactive isotope scan. There must be no other primary tumor.

When these conditions are met, a card is drawn which allocates the patient into one or other of the two groups. When preoperative irradiation is ordered, operation is scheduled 4 weeks after the completion of radiation therapy. To date, abdominoperineal resection has been the procedure of choice, although consideration is being given to anterior resection when appropriate.

Cooperating surgeons are located throughout the state of Connecticut with whom we have established a working relationship, and have to date contributed 6 of the 28 patients whom we are reporting. In all instances, the irradiation was carried out at the Yale-New Haven Medical Center. The 21 patients primarily seen at our Medical Center include those who were admitted to our affiliated Veterans Administration Hospital in West Haven. The outside cooperating surgeons are Drs. John D. Booth, Robert Grossman, and Felix Tomaino of the Danbury Hospital and Drs. William H. Curley, Jr. and Michael A. Dean of St. Vincent's Hospital in Bridgeport.

MATERIAL AND METHODS

Eighteen of 19 patients received a full course of irradiation. The nineteenth died of myocardial infarction immediately after the beginning of radiation therapy. The treatment plan delivers a dose of 4,500 rads in $4\frac{1}{2}$ weeks to the entire pelvis by means of anterior and posterior portals using a 6 mev. linear accelerator. The field (Fig. 1), which measures 15×22 cm. overall, covers the entire true pelvis as well as a narrow extension superiorly which includes the body of L4. The radiation is well tolerated and in all patients, other than the one with a myocardial infarction, treatment was completed. Diarrhea was experienced by 70 per cent of the patients

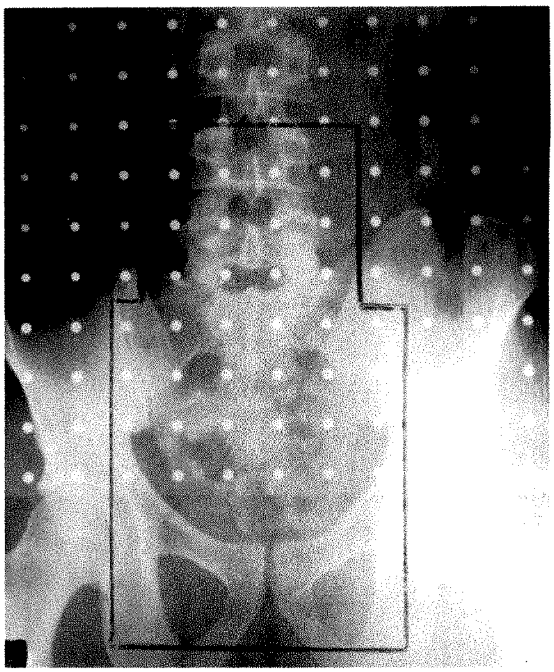

FIG. 1. Opposing anteroposterior portals are used with a 6 mev. linear accelerator; 4,500 rads tumor dose is delivered in $4\frac{1}{2}$ weeks.

and was of moderate intensity. It was readily controlled by paregoric. Two patients complained of dysuria. In 2 cases, a moist epidermitis developed in the gluteal crease which healed promptly.

Of the 18 patients who completed radiation therapy, 17 were found to be resectable. The patient with the one nonresectable tumor was found to have a frozen pelvis at the time of operation. Two preirradiation, inoperable patients, one clinically so, and one determined by previous exploratory laparotomy, became operable after irradiation was given. At operation none of the cases presented difficulties which interfered with resection. One of the authors (M.A.H.) expressed the opinion that he found no difference between an irradiated and a nonirradiated pelvis. One patient in whom extensive fibrosis was found in the pelvis had a long history of diverticulitis. In 4 other patients, mild fibrosis was observed. Three patients had bleeding problems. In one, abnormal ooze was observed; in one, persistent bleeding occurred from some obscure point; and in one, increased bleeding occurred from the presacral veins. All survived the procedure; however, the rate of postoperative complications in the irradiated group was 66 per cent and included 3 postoperative deaths. Although this figure is high, it compares with the general rate of complications for abdominal perineal resection without previous irradiation. Death in one patient occurred after gastric ulcer, renal failure, electrolyte imbalance, and septicemia. In a second patient, shock of unknown cause ended in death. In the third patient, sepsis, hypotension, and renal failure resulted in death. A complete list of postoperative complications is seen in Table I. One patient had developed a late complication 2 years after the combined procedure. He was readmitted with intestinal obstruction due to extensive adhesions. The patient has improved following operative lysis of these adhesions.

Table I

COMPLICATIONS*

	Surgery Alone	Irradiation and Surgery
Cardiovascular		
Cerebrovascular accident	1 case	—
Shock	—	1 case
Gastrointestinal		
Colostomy necrosis	1 case	—
Gastritis	—	1 case
Leakage at intestinal suture line	1 case	—
Perforated gastric ulcer	—	1 case
Peritonitis	1 case	—
Poorly functioning colostomy	—	1 case
Small bowel fistula	—	1 case
Small bowel obstruction	—	1 case
Stress gastric ulcer	1 case	—
Genitourinary		
Cystitis	1 case	4 cases
Renal failure	—	2 cases
Pulmonary		
Pneumonia	2 cases	—
Pulmonary edema	—	1 case
Infections		
Septicemia	2 cases	2 cases
Wound infections	8 cases	7 cases
	18 Complications in 6 of 9 Patients	22 Complications in 12 of 18 Patients

* Although the complications are high, they are similar to those which are reported in large series of patients treated by surgery alone.

ANATOMIC STUDIES FOLLOWING RADIATION THERAPY AND OPERATION

Of the 19 cases treated with preoperative irradiation with the intent to perform an operative resection, 2 patients did not receive a resection. One of these died of a myocardial infarction during irradiation, and the second was not resectable because a frozen pelvis was found at laparotomy. This left 17 cases which were reviewed anatomically following radiation therapy. They were compared with the 8 cases of

surgical resection of adenocarcinoma of the rectum which did not receive preoperative irradiation as part of the randomized series. (The ninth case in the operation only group was not resectable.) A diagnosis of adenocarcinoma of the rectum had been made before irradiation in each case. These slides were reviewed for this report and found to contain tumor.

GROSS TUMOR RESPONSE TO IRRADIATION

Patients were sigmoidoscoped before the beginning of treatment, during the course of treatment, and immediately preoperatively. Impressive regression of tumor was noted in some. In 5 cases the tumor reduction was from 75 to 100 per cent. Three of these 5 showed complete disappearance of tumor. In 5 cases the reduction was from 50 to 74 per cent; in 2 patients the reduction was between 25 to 49 per cent. In 6 patients the reduction amounted to from 0 to 24 per cent of the original tumor size. Two of these 6 showed no gross regression.

MICROSCOPIC EXAMINATION

Sections of the main tumor mass and associated tissues were reviewed microscopically and several observations were made. All showed at least some destruction of the primary tumor even in the 2 which showed no gross regression. Radiation effect was graded on a I to IV basis with Grade I equal to minimal change, Grade II equal to moderate change, and Grade III equal to marked change. Grade IV indicates complete absence of tumor.

It is understood that the changes noted within a particular tumor are not necessarily uniform. In some specimens portions of the mass revealed marked disintegration, while adjacent portions showed little alteration in the cellular patterns. Microscopic grading of the response to radiation, therefore, represents the pathologist's overall impression. The changes interpreted as secondary to radiation were determined by comparing the irradiated tumors with those removed operatively without preoperative irradiation, and reviewing the literature.[6,15,16]

The changes observed in irradiated tumors included:

1. The earliest changes appear to be marked swelling of the nucleus and cytoplasm of the tumor cells.
2. Nuclear chromatin clumping and irregularity of the nuclear membrane.
3. Granular cytoplasm which stains more eosinophilic and tends to be more vacuolated. Cells are fragmented, reduced, and shrunken in size with nuclear material aggregated in pyknotic clumps.
4. Cell fusion with loss of cellular outlines.
5. Necrotic ghost cells occasionally seen, particularly associated with large regions of necrosis.
6. Some portions of tumor reveal large regions of microscopic necrosis.
7. In some no recognizable tumor is seen.
8. Tumor which is destroyed may show a reversion toward normal mucosa and submucosal structure, or it may show varying amounts of fibrosis. Mucin lakes, which can be seen in nonirradiated rectal cancers, occurred with greater frequency in these irradiated cases.

Of the 17 cases available for review, 3 showed minimal microscopic changes and 2 showed complete absence of tumor. Seven fell in the moderate and 5 in the marked radiation effect category. It should be re-emphasized that the original biopsies on the 2 cases of complete absence of tumor histologically in the surgical specimen did contain adenocarcinoma. Extensive necrosis with marked fibrosis of the tumor was more common in the irradiated series when compared with the controls. This replacement of dead and dying tumor tissue by reactive fibrosis accounts for failure to observe a decrease in the gross tumor size commensurate with microscopic evidence of tumor cell destruction.

Positive regional lymph nodes were found in 3 patients. In a fourth patient, one

lymph node was questionably positive for tumor. In a fifth patient, the material was inadequate for lymph node evaluation. In the remaining 12 specimens the lymph nodes were free of tumor and were either markedly reduced in size or lymphoid tissue was found only with great difficulty. In 2 patients, tumor had spread through the thickness of the bowel but tumor could not be identified within lymphatic tissue.

The surgical specimens were classified by Dukes' method.[4,5] In the preoperatively irradiated group, there were 9 Class A. (Two of these contained no tumor—a category which Dukes could not include since all of his specimens necessarily had to contain tumor!) There were 3 Class B and 4 Class C. The patient with questionable lymphatic involvement mentioned above is considered positive (Table II).

The remaining tumor and adjacent colon revealed marked edema, inflammatory infiltrates, and extensive fibrosis. Collagenized material appeared to be deposited in the sites of previous edema and replaced large portions of what was apparently necrotic tumor. The blood vessels also showed changes. The earliest changes appeared to be edema of the blood vessel walls followed by intimal and subintimal proliferation of endothelial cells and fibroblastic tissue. Many vessels appeared to be thickened with reduction in the lumen. Thrombosis was not frequent in the present series, only being found unequivocally in 1 case.

Table II

MICROSCOPIC PATHOLOGY OF RESECTED SPECIMENS

	No. Cases	Positive	Negative
Protocol Study—Surgical Group			
Primary	8*	8	—
Regional Lymph Nodes	8	6	2
Protocol Study—Preoperative Irradiation Group			
Primary	8†	8	—
Regional Lymph Nodes	8	2	6
All Preoperative Irradiation Cases			
Primary	17‡	15	2
Regional Lymph Nodes	17	4	13

* One case not resectable.
† One case not resectable.
‡ One case died of myocardial infarction during irradiation.
Note: There is a reduction in the relative number of positive and negative lymph nodes in the cases which had preoperative irradiation. See text for the shift in the distribution of pathology as classified after Dukes in the preoperative irradiation group.

The microscopic changes present in the adjacent resected portions of rectum are essentially similar to those reported by Gelfand *et al.*[8] In many of the cases resected earlier following irradiation of the region, the mucosa revealed the presence of crypt abscesses composed almost entirely of eosinophils. A marked increase in focal tissue eosinophilia was also noted. The surface and crypt epithelium revealed a change in the typical columnar epithelium to a more cuboidal form with larger nuclei. Mucus production appeared to be reduced with occasional distended goblet cells. Submucosal edema was present in many of the earlier cases. In the cases resected at a later time interval, following irradiation, most of the mucosal structures had returned to normal. Some submucosal fibrosis was present and lymphocytic elements, particularly in the lamina propria, appeared markedly reduced. In addition, the lymph nodes found in the specimens were reduced in size compared to normal material. The details of the anatomic findings will be amplified in a subsequent report.[19]

Four patients are reported which represent the typical findings in the 4 categories of response to radiation therapy: minimal, moderate, marked and complete absence of tumor microscopically.

REPORT OF CASES

Case I. *Minimal microscopic radiation change.* Patient S. G., a 66 year old white male, who in September 1965 was found to have a fungating mass involving the anterior half of the rectum. Biopsy of this mass was reported as poorly-differentiated adenocarcinoma (Fig. 2). He received 4,500 rads tumor dose in 30 days with a gross tumor reduction of about 80 per cent.

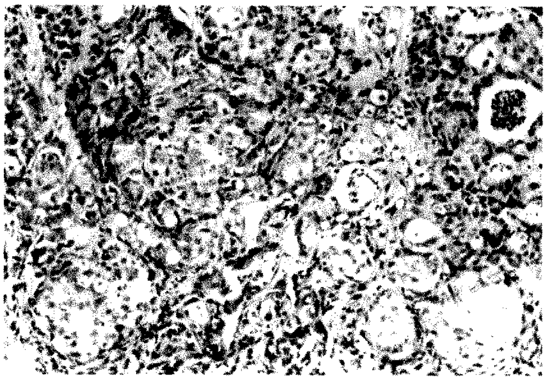

FIG. 2. Case I. Preirradiation biopsy of the rectal tumor showing moderately poorly-differentiated adenocarcinoma. (Hematoxylin and eosin, ×105.)

FIG. 4. Case II. Preirradiation biopsy of rectal tumor showing moderately differentiated rectal adenocarcinoma. (Hematoxylin and eosin, ×105.)

Four and one-half weeks later, he underwent an abdominal perineal resection. Residual tumor was present in the rectum showing minimal radiation change (Fig. 3). The regional lymph nodes were negative. Several months later, he developed local recurrence and distant metastases. He died in January 1967.

CASE II. *Moderate microscopic radiation change.* Patient R. M., a 51 year old white male, who in September 1964 was found to have a 5×5 cm. exophytic rectal tumor. Biopsy was reported as adenocarcinoma (Fig. 4). He underwent an exploratory laparotomy and the tumor was found to be nonresectable because of extensive anterior fixation. He received 4,500 rads tumor dose in 30 days. The gross tumor response to the radiation was estimated to be about 75 per cent regression. Four weeks later an abdominal perineal resection was performed. Residual tumor was present in the rectum showing moderate radiation change (Fig. 5), but the regional lymph nodes were negative. Two years later, the patient was reoperated because of intestinal obstruction due to extensive abdominal adhesions. No evidence of tumor was found. He is still alive 3 years after diagnosis was made.

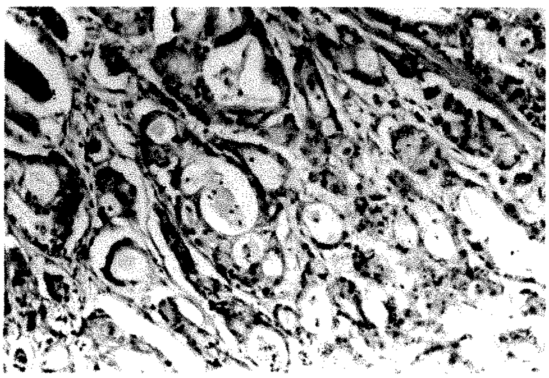

FIG. 3. Case I. Minimal microscopic radiation changes. Section of tumor mass resected 33 days following irradiation. Note swelling of cytoplasm and nuclei of tumor cells. Some minimal vacuolization of the cytoplasm and loss of cytoplasmic boundaries are seen. (Hematoxylin and eosin, ×105.)

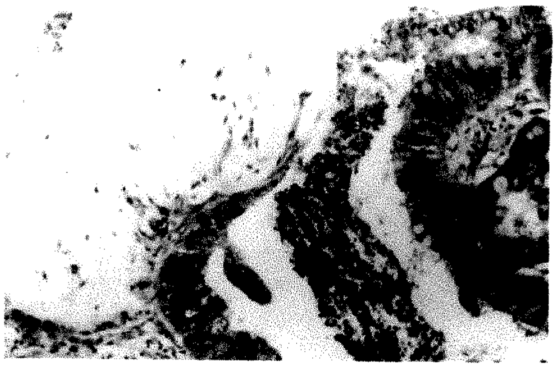

FIG. 5. Case II. Moderate microscopic radiation change. Section of tumor mass resected 28 days following radiation therapy. Note swelling of nuclei with clumping of nuclear chromatin and irregularity of nuclear outlines. The cytoplasm is swollen, appears mildly granular and vacuolated. Minimal cell fusion and loss of cellular outlines are also seen. Focal necrosis is present. The clear zone in the upper left hand portion of the picture represents a mucin lake. (Hematoxylin and eosin, ×105.)

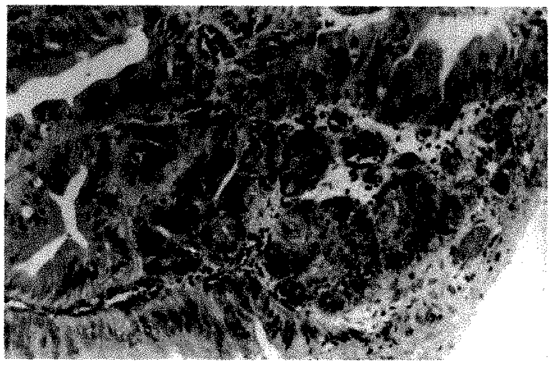

Fig. 6. Case iii. Preirradiation biopsy of rectal tumor showing well-differentiated adenocarcinoma. Note number of mitoses present. (Hematoxylin and eosin, × 105.)

Fig. 7. Case iii. Marked microscopic radiation change. Section of residual tumor in rectal wall removed 34 days following irradiation of rectal carcinoma. On the left, note nuclear chromatin clumping and irregular nuclear membranes. Some nuclear material aggregated in clumps is also seen. On the right, some cells reveal cytoplasm which is granular, stains more eosinophilic, and the cytoplasmic boundaries are indistinct resulting in cell fusion. (Hematoxylin and eosin, ×105.)

Case iii. *Marked microscopic radiation change.* Patient J. M., a 55 year old white female was found to have an extensive rectal carcinoma in July of 1963. It involved the anterior two-thirds of the rectal wall with infiltration of the rectovaginal septum, and involved the posterior half of the vaginal wall. Biopsy was reported as well-differentiated rectal adenocarcinoma (Fig. 6). She received preoperative irradiation, 4,000 rads tumor dose in 25 days. Five weeks later, she underwent abdominal perineal resection. No gross tumor was present in the rectum; however, microscopic nests of tumor cells showing marked radiation change were found in the rectum and lymph nodes (Fig. 7). The patient did well until $2\frac{1}{2}$ years later, when she developed metastases in the bony pelvis. She is alive at the time of the writing.

Case iv. *Total radiation destruction of tumor.* Patient J. S., a 72 year old white male who in January 1967 was found to have a polypoid lesion, 11 cm. above the anus. This tumor was partially excised and reported as adenocarcinoma (Fig. 8). At the same time, an epidermoid carcinoma of the lung was discovered for which he underwent a lobectomy. A course of preoperative irradiation to the rectum was given, 4,250 rads tumor dose in 30 days. Four weeks later, abdominal perineal resection was done and no evidence of tumor was found on microscopic examination in multiple sections of the rectum or regional lymph nodes (Fig. 9). Recently, the patient developed an enlarged hilum and liver, and required radiation therapy to ribs and shoulder where metastases were assumed to be secondary to a lung tumor. He had no symptoms in the pelvic region. He expired in August 1967. No autopsy was performed.

DISCUSSION

Replacement of tumor cells by reactive fibrosis is a common finding microscopically. We were struck by the observation that tumor-cell destruction occurred in all irradiated specimens even when there was no significant decrease in the gross size of the lesion. The reason that this loss of cells could not be correlated with the gross volume was that fibrotic connective tissue

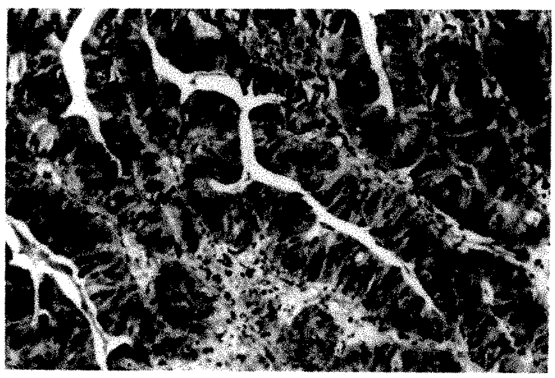

Fig. 8. Case iv. Preirradiation biopsy of rectal tumor showing moderately well-differentiated adenocarcinoma. (Hematoxylin and eosin, ×105.)

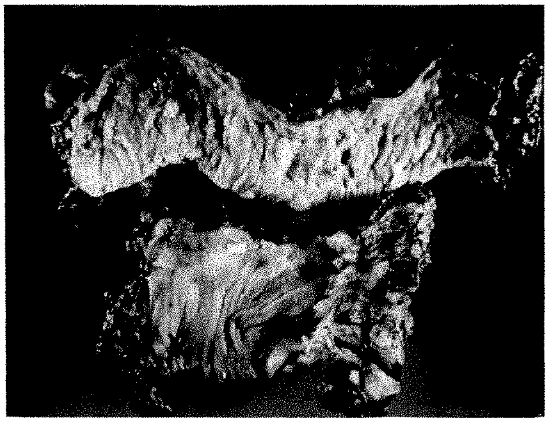

Fig. 9. Case iv. Total radiation destruction of tumor. Photograph of resected specimens showing small induration in the mucosa of the rectum. This was the site of a biopsy taken one week before resection. Multiple sections from this and adjacent regions and lymph nodes failed to reveal any evidence of residual tumor.

had replaced the destroyed portions of tumor. Every specimen showed evidence of destruction of cells to some degree following irradiation. Tumors of all degrees of differentiation showed evidence of cellular destruction, although in general the effect was more marked in the well-differentiated tumors. Furthermore, destruction of tumor cells was noted in the lymph nodes as well as in the primary lesions. This lack of correlation between postirradiation tumor masses and the degree of cellular destruction observed in this series of cases had been noted previously by our group in lung carcinoma.[10]

These benefits could arise from preoperative irradiation of rectal carcinoma if given to the volume illustrated in Figure 1. Tumors might be rendered resectable which might be fixed at the time of exploration; there could be reduction of the relatively high incidence of recurrence seen in tumors of the lower rectum; and lymph node metastases in the regional drainage area could be reduced or eliminated. For this reason, the entire true pelvis is treated, and the lymph nodes at the bifurcation of the aorta are included in the field. Since we now have a total experience with preoperative irradiation of 22 cases (including those which came onto the service after this report was drawn up), we feel confident that the dose schedule of 4,500 rads in $4\frac{1}{2}$ weeks is well tolerated. We are now extending the lumbar portion of the radiation field superiorly to the middle of the second lumbar vertebra so that the lymph nodes which accompany the inferior mesenteric artery will be included. At this upper level, we should be irradiating the regional drainage where clinical metastases are seen in approximately 99 per cent of patients.[1,2,3,12,14,18]

The number and type of complications (Table I) is not significantly different from those reported by Levine and Abramson.[11] That report indicates 228 cases out of a total of 358 patients (63.7 per cent) with complications. The 22 complications in this report were in 12 of 18 patients (66.6 per cent) given preoperative irradiation. In our own randomized series, the two groups, although each small in number, developed essentially the same rate and type of complication.

One striking preliminary observation is the distribution of the patients who receive preoperative irradiation in the Dukes classification. Whereas one would expect 50 per cent of the specimens to show evidence of malignant cells in the lymph nodes (Dukes C), only 5 of the 18 patients who were explored showed evidence of lymph node involvement. Nine of the specimens were Dukes A (tumor limited to the rectum). In 2 of these, no tumor could be found in the resected specimen. Four were Dukes B (extension to perirectal fat), and 5 were Dukes C (extension to lymph nodes). In the surgery only group, one specimen was a Dukes A, one was a Dukes B, and 7 were Dukes C.

We cannot speak of survival in the preliminary report because of the small numbers involved and the lack of an extended follow-up. The high degree of cellular lethality demonstrated in these specimens, both in the primary tumor and in the lymph nodes in those given preoperative

irradiation suggests to us that continuation of the study is warranted.

CONCLUSIONS

Preoperative irradiation is a reasonable approach for rectal carcinoma. Our philosophy of treating the primary tumor and all the lymph node bearing regions up to the fourth lumbar vertebra to a dose of 4,500 rads has proven to be well tolerated by the patients and did not interfere with the subsequent surgical procedure.

A strictly randomized study of preoperative irradiation *vs.* surgery alone is currently underway to evaluate the combined procedure. At the present time, we are not able to report meaningful survival figures because of the short follow-up period and the small number of patients.

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SEMINOMA OF THE TESTIS: ANALYSIS OF TREATMENT SUCCESS AND FAILURE*

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TESTICULAR tumors comprise less than 1 per cent of all malignant tumors, but are not uncommon in military personnel because of the age of the patient population at risk. Dorn[2] has reported that testicular tumors are the most common type of malignancy seen in males between 29 and 34 years of age. During the period from January 1, 1940, through December 31, 1965, approximately 800 testicular tumors have been seen at Walter Reed General Hospital, Washington, D. C. The purpose of this paper is to present an analysis of those cases seen during this period, which have been categorized histologically as pure seminoma. Primary consideration has been given in this study to determine which treatment methods have led to success or failure.

PATHOLOGY

Most American pathologists classify testicular neoplasms into two major categories: germinal neoplasms and nongerminal neoplasms. More than 95 per cent of testicular neoplasms encountered in general pathology practice belong within the germinal group. These germinal neoplasms are presumed to arise from primitive germ cells or primordial sex cells of the seminiferous tubules. Such cells are regarded as totipotential and thus, when undergoing malignant neoplastic change, may theoretically form any type of cancer. Seminomas of the testis, while considered of germ cell origin, are an apparent exception to this concept of totipotentiality and seminomas *per se* are considered distinct entities separable histopathologically as well as biologically from the other more obviously interrelated germinal neoplasms, *e.g.*, embryonal carcinoma, teratoma-teratocarcinoma, and choriocarcinoma.

The general category of seminoma has been further subdivided into three groups as follows: (1) classical seminoma; (2) anaplastic seminoma; and (3) spermatocytic seminoma. A detailed description of the histopathology in each of these subgroups is to be published.[4] The 277 cases of seminoma in the present series consist of 250 classical seminomas, 26 anaplastic seminomas and 1 atypical or spermatocytic seminoma.

CLINICAL MATERIAL

The data in this series have been compiled from 277 consecutive patients having a pure seminoma cell line in the orchiectomy specimen. Initially, the histologic material in all cases treated at Walter Reed General Hospital during the time of the study with a clinical diagnosis of seminoma, whether pure or mixed with other cell lines, was re-examined. The initial microscopic material was obtained for review in all cases except 2 from the Pathology Departments at Walter Reed General Hospital or the Armed Forces Institute of Pathology. In these 2 cases written reports are available, but the initial histologic material has not been located.

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In the subsequent course of determining the fate of these patients, a total of 10 have been lost to follow-up (96 per cent follow-up rate). A total of 220 patients are now at risk 5 years after their initial diagnoses.

There were a total of 272 Caucasian patients and 5 Negro patients. The right testicle was involved in 153 instances, the left in 124, and there were 6 cases of bilateral involvement. There were 22 cases of undescended testicle with an orchiopexy having been performed in 10 instances. Figure 1 shows the age incidence by decades.

In an effort to more fully evaluate the treatment modalities utilized in this series, a system of staging was utilized and all cases were retrospectively staged. This staging system is shown in Table I. Of the total 277 patients, there were a total of 230 Stage IA, 14 Stage IB, 22 Stage II, and 11 Stage III patients.

TABLE I

STAGING SYSTEM OF TESTICULAR TUMORS AT WALTER REED GENERAL HOSPITAL

IA	Tumor confined to one testis. No clinical or radiographic evidence of spread beyond. May include excretory or retrograde urography, lymphangiography, inferior venacavagraphy and chest roentgenography.
IB	As in IA but found to have histologic evidence of metastases to iliac or para-aortic lymph nodes at time of retroperitoneal lymph node dissection.
II	Clinical or radiographic evidence of metastases to femoral, inguinal, iliac, or para-aortic lymph nodes. No demonstrable metastases above the diaphragm or to visceral organs.
III	Clinical or radiographic evidence of metastases above the diaphragm or other distant metastases to body organs.

METHOD OF TREATMENT

The present series extends over a period of 26 years and includes the participation of a number of different urologists and radiotherapists. It is not surprising to find that treatment has been variable during this time interval. In earlier years, almost all patients had orchiectomy followed by retroperitoneal lymphadenectomy and postoperative irradiation. In more advanced cases the lymphadenectomy was omitted. In later years, the retroperitoneal lymphadenectomy was discontinued except for the anaplastic seminomas (this has recently also been discontinued). It is convenient, although far from ideal because of selection, to find that approximately ½ of the cases at risk at least 5 years fall into each of the two groups.

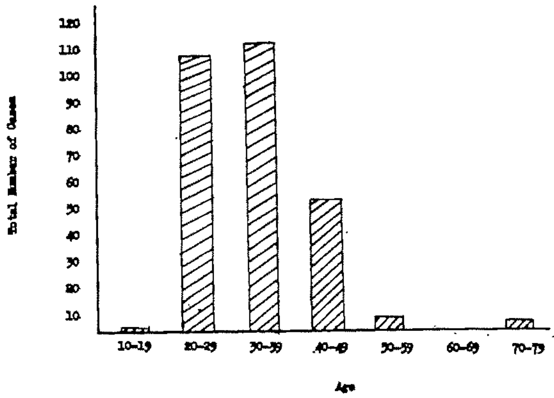

FIG. 1. Age incidence by decades is shown in 277 cases of seminoma of the testis seen at the Walter Reed General Hospital during the years 1940 to 1965.

A total of 276 patients have received irradiation to the lymph node draining areas of the testicle. In earlier years only the inguinal, iliac, and para-aortic lymph nodes were included. In later years the mediastinal and left supraclavicular lymph nodes were also irradiated in all cases. In 87 per cent of patients supervoltage equipment was utilized. This included 1 mvp. roentgen ray with 3.6 mm. Pb half value layer, 2 mvp. roentgen ray with 7.6 mm. Pb half value layer, and cobalt 60 teletherapy with 11 mm. Pb half value layer. Orthovoltage equipment consisted of 220 kvp. roentgen ray with 2 mm. Cu half value layer. In the majority of patients doses ranged from 2,000–3,000 r to each field in 2 to 4 weeks, although doses in excess of this were used very early in the series.

TABLE II

SEMINOMAS

(WALTER REED GENERAL HOSPITAL, 1940–1960)

Results by Staging and Treatment

	Orchiectomy+Irradiation		Orchiectomy+Lymphadenectomy +Irradiation		Total	
Stage	Relative 5 Yr.	Absolute 5 Yr.	Relative 5 Yr.	Absolute 5 Yr.	Relative 5 Yr.	Absolute 5 Yr.
IA	78/80= 98%	78/89= 88%	87/88= 99%	87/92= 95%	165/168=98%	165/181=91%
IB	5/5 =100%	5/5 =100%	7/8 = 88%	7/9 = 78%	12/13 = 92%	12/14 =86%
II	9/10= 90%	9/12= 75%	1/1 =100%	1/1 =100%	10/11=91%	10/13 =77%
III	2/11= 18%	2/11= 18%	0	0	2/11 =18%	2/11 =18%
Total	94/106= 89%	94/117= 80%	95/97= 98%	95/102=93%	189/203=93%	189/219=86%

RESULTS

There are a total of 220 cases at risk for at least 5 years. Of these, 189 patients are known to be alive and free of tumor; 15 are known to have died from seminoma; 8 are dead from intercurrent disease; and 8 patients have been lost to follow-up. This results in a relative 5 year survival of 93 per cent and an absolute 5 year survival of 86 per cent. The results by staging and method of treatment are shown in Table II. A total of 117 patients were treated by orchiectomy and irradiation, whereas 102 patients had orchiectomy followed by lymphadenectomy and postoperative irradiation. One patient was treated by orchiectomy and chemotherapy only.

Of the total number of 277 cases in this series, 26 were diagnosed as being anaplastic seminoma of which 23 were at risk a minimum of 5 years. Of these, 17 are living free of tumor, 5 are dead from tumor, and 1 is lost to follow-up. This results in a relative 5 year survival of 77 per cent and an absolute 5 year survival of 74 per cent. The results by staging and method of treatment in the anaplastic seminoma group are shown in Table III.

DISCUSSION

In the past 25 years various reported series of testicular seminoma have shown an improvement in survival figures. In a review of a collected series of 396 testicular

TABLE III

ANAPLASTIC SEMINOMA

(WALTER REED GENERAL HOSPITAL, 1940–1960)

Results by Staging and Treatment

	Orchiectomy+ Irradiation		Orchiectomy+ Lymphadenectomy+ Irradiation		Total	
Stage	Relative 5 Yr.	Absolute 5 Yr.	Relative 5 Yr.	Absolute 5 Yr.	Relative 5 Yr.	Absolute 5 Yr.
IA	4/4 =100%	4/4 =100%	9/10= 90%	9/11= 82%	13/14= 93%	13/15= 87%
IB	0	0	2/2 =100%	2/2 =100%	2/2 =100%	2/2 =100%
II	2/2 =100%	2/2 =100%	0	0	2/2 =100%	2/2 =100%
III	0/4 = 0%	0/4 = 0%	0	0	0/4 = 0%	0/4 = 0%
Total	6/10= 60%	6/10= 60%	11/12= 92%	11/13= 85%	17/22= 77%	17/23= 74%

tumors by Gordon-Taylor and Wyndham[8] up to 1941, the 5 year survival rate for seminoma was 52.5 per cent. In 1951, Boden and Gibb[1] pointed out the value of staging in prognosis. In cases presenting with tumor confined initially to the testis (Stage I), there was an 80 per cent 5 year survival, whereas metastases to the retroperitoneal lymph nodes (Stage II) resulted in only a 41 per cent 5 year survival. When distant metastases occurred (Stage III), only 12 per cent 5 year survival was found. More recently, Notter and Ranudd[5] found an overall 5 year survival of 75 per cent in a series of 173 seminoma patients. In Stage I there was an 88 per cent 5 year survival, whereas in Stage II there was 39 per cent and in Stage III 20 per cent. In both the series by Boden and Gibb[1] and by Notter and Ranudd[5] the treatment was by orchiectomy and postoperative irradiation without lymphadenectomy.

In an earlier publication from Walter Reed General Hospital, Patton and Mallis[6] reported a 96 per cent relative and an 83 per cent absolute 5 year survival in 100 seminoma cases treated by orchiectomy, lymphadenectomy and postoperative irradiation. The question arises as to the explanation of these improved results as reported by Patton and Mallis.[6] Does the lymphadenectomy *per se* explain these results or were they influenced by selection and staging? An examination of the data in Tables II and III, which include the 100 cases of Patton and Mallis,[6] appears to warrant several conclusions. The first is that the addition of a retroperitoneal lymph node dissection following orchiectomy combined with postoperative irradiation, has not improved survival figures as compared with orchiectomy and irradiation alone when the stage of the disease is taken into consideration. The second is that the prognosis for the classical seminoma and the anaplastic seminoma is quite comparable when the stage of disease is again taken into consideration. Likewise, the addition of a retroperitoneal lymph node dissection to orchiectomy and postoperative irradiation has not improved survival figures in the case of anaplastic seminoma.

In spite of the favorable results in this series, there are 19 cases known to have died as a result of tumor; 15 of these are at risk longer than 5 years (Table IV), and 4 cases are at risk less than 5 years (Table V).

As might be anticipated, the majority of the patients that died from tumor were advanced cases when first seen. They included 7 Stage I, 2 Stage II, and 10 Stage III cases. A total of 6 of these 19 cases were anaplastic seminoma or a 31 per cent incidence, as compared to only a 10 per cent incidence in the entire series. This would tend to incriminate the anaplastic seminoma as being a more aggressive tumor, but not any less radiosensitive.

Of the 19 patients who died from seminoma, a total of 17 patients had autopsies. In 3 cases testicular tumor metastases, other than the original diagnosis of seminoma, were found. Two of these cases had metastases with mixtures of choriocarcinoma and embryonal carcinoma and 1 was embryonal carcinoma alone. A fourth case had anaplastic seminoma metastases and questionable sarcoma metastases, suspected of being radiation induced, at 77 months following the original diagnosis.

In these 4 cases with metastases other than seminoma, the question can be raised whether mixed tumors were present initially in the testicular tumor and not seen. The original biospy material was reviewed with this in mind and mixed tumors were not found in the testis specimens. However, the original tumor specimens had been discarded and only the slides and tissue blocks from the original material were available for review. If these 4 cases represent totipotency for seminoma to change into other forms, it represents an incidence of only 2 per cent in the 220 cases at risk 5 years.

It is of considerable interest that in 7 Stage I cases (6 Stage IA and 1 Stage IB) in the series that died from tumor, only 2 were given prophylactic irradiation to the lymphatics of the mediastinum and left supraclavicular regions. In these 2 cases the

Table IV

SEMINOMA TUMOR DEATHS AT RISK GREATER THAN 5 YEARS

Case No.	Stage	Age (yr.)	Time from Diagnosis to Death (mo.)	Pathology Diagnosis of Testicle	Pathology Diagnosis at Autopsy	O+R[1]	O+L +R[2]	Area Treated Initially	Dose (r)	Time of Radiation Treatment (wk.)
3	IA	25	9	Anaplastic seminoma	No autopsy		+	A,[3] B[4]	3,700; 5,400	12; 13
7	IA	22	15	Seminoma	Seminoma	+		A, B	2,000; 2,000	2; 2
11	IA	27	77	Anaplastic seminoma	Anaplastic seminoma Sarcoma?	+		A, B	3,200; 5,000	6; 8
13	IA	25	13	Seminoma	Seminoma	+		A, B	2,000; 2,000	2; 2
6	IB	35	16	Seminoma	Seminoma		+	A, B	2,200; 5,600	2; 7
1	II	30	41	Seminoma	Seminoma	+		A, B	3,600; 5,700	8; 12
2	III	27	5	Anaplastic seminoma	Anaplastic seminoma	+		A, B	2,000; 3,000	2; 3
4	III	31	1	Anaplastic seminoma	Choriocarcinoma Embryonal			0	0	
5	III	44	9	Seminoma	Seminoma	+		A, B, C,[5] D[6]	2,000; 2,000 2,000; 2,000	3; 3 3; 3
8	III	25	18	Anaplastic seminoma	Choriocarcinoma Embryonal		+	A, B, C, D	2,000; 4,000 2,000; 2,000	2; 4 2; 2
9	III	23	2	Anaplastic seminoma	Embryonal	+		A, B, D	2,000; 2,300 2,000	2; 3 2
10	III	41	24	Seminoma	No autopsy	+		A, B, D	3,800; 4,300 3,000	11; 12 3
12	III	30	4	Seminoma	Seminoma	+		A, B, C, D	2,000; 5,800 2,000; 3,000	2; 4 2; 3
14	III	39	43	Seminoma	Seminoma	+		A, B, C, D	2,000; 2,000 2,000; 2,500	2; 2 2; 3
15	III	45	2	Seminoma	Seminoma	+		A, B	2,000; 2,300	2; 3

[1] O+R=Orchiectomy, irradiation.
[2] O+L+R=Orchiectomy, lymphadenectomy, irradiation.
[3] A=Inguinal, iliac lymph nodes.
[4] B=Para-aortic lymph nodes.
[5] C=Mediastinal lymph nodes.
[6] D=Left supraclavicular lymph nodes.

recurrent tumor appeared a short time following treatment and was outside the irradiated fields. In 1 case this occurred in the right lower lobe of the lung and in the second case in the liver. It is presumed that these metastases were present when the patient was initially treated, but were undiagnosed.

During the early years in this series, irradiation was only given to the inguinal, iliac, and para-aortic lymph node drainage areas. The mediastinal and supraclavicular lymph nodes were irradiated only when positive metastases were found in the inguinal, iliac, and para-aortic lymph nodes. In the 5 Stage I deaths not given prophylactic irradiation to the mediastinum or supraclavicular regions, the tumor metastases first ap-

TABLE V

SEMINOMA TUMOR DEATHS AT RISK LESS THAN 5 YEARS

Case No.	Stage	Age (yr.)	Time from Diagnosis to Death (mo.)	Pathology Diagnosis of Testicle	Pathology Diagnosis at Autopsy	O+R[1]	O+L +R[2]	Area Treated Initially	Dose (r)	Time of Radiation Treatment (wk.)
16	II	25	17	Seminoma	Seminoma, embryonal	+		A,[3] B,[4] C,[5] D[6]	2,000; 2,000 2,000; 2,000	2; 2 2; 2
17	IA	41	27	Seminoma	No autopsy	+		A, B, C, D	2,000; 2,000 2,000; 2,000	2; 2 2; 2
18	III	33	22	Seminoma	Seminoma	+		A, B, C, D	2,000; 2,000 2,000; 2,000	2; 2 2; 2
19	IA	25	20	Seminoma	Seminoma	+		A, B, C, D	2,000; 2,000 2,000; 2,000	2; 2 2; 2

[1] O+R=Orchiectomy, irradiation.
[2] O+L+R=Orchiectomy, lymphadenectomy, irradiation.
[3] A=Inguinal lymph nodes.
[4] B=Para-aortic lymph nodes.
[5] C=Mediastinal lymph nodes.
[6] D=Left supraclavicular lymph nodes.

peared in these areas. Later, additional irradiation controlled these metastases for various periods of time, but subsequent distant metastases resulted in the death of these patients.

The question arises as to the possible complications of prophylactic irradiation to a total dose of 2,000 r in 12 to 14 days to the mediastinum and supraclavicular regions. To date there have been no complications resulting from such treatment. Consideration was especially given to the possible development of radiation pneumonitis and leukemogenesis, but no such complications have been found.

In the present series there were 47 cases with proven metastases. Based on a 10 per cent incidence of metastases in Stage I cases when lymphadenectomy was done, the total estimated number of cases with metastases would be 62. Analysis of the response of lymph node metastases from seminoma has indicated that an optimum dose of radiation is 3,000 r in 3 weeks with supervoltage radiation. Instances of local recurrence have been found after 2,000 r in 2 weeks for clinically positive lymph node metastases, but none after doses of 3,000 r unless widespread metastases were present and reseeding from distant sites may have occurred.

CONCLUSIONS

1. Seminoma is a highly radiocurable tumor and prognosis is directly related to the extent of disease when first seen. Tumor staging is valuable in estimating prognosis.

2. A pure seminoma is a distinct entity and the so-called anaplastic seminoma has the same prognosis as a classical seminoma when staging is taken into consideration.

3. Prophylactic irradiation of mediastinal and left supraclavicular lymphatics in addition to inguinal and abdominal para-aortic lymph nodes following orchiectomy appears warranted and has been performed without complications. A minimum tumor dose of 2,000 r in 2 weeks with supervoltage radiation has been adequate for prophylactic irradiation in such cases.

4. A minimum tumor dose of 3,000 r in 3 weeks for clinical metastases in lymph

nodes is necessary for sterilization of such lymph nodes.

SUMMARY

A review of 277 cases of seminoma of the testis is presented with particular reference to comparison of treatment methods. The relative 5 year survival in 220 cases has been found to be 93 per cent and the absolute 5 year survival is 86 per cent. The results in cases with similar staging show no difference when treated by orchiectomy and irradiation *versus* orchiectomy, retroperitoneal lymphadenectomy and irradiation. The so-called anaplastic seminoma has been found to respond to treatment in a manner similar to the classical form of seminoma. The recommended treatment of choice for seminoma of the testis is orchiectomy followed by postoperative irradiation to the lymph node draining areas including the inguinal, iliac, para-aortic, mediastinal and left supraclavicular areas.

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CANCER OF THE OVARY*

A TWENTY-ONE YEAR STUDY OF 1,722 PATIENTS TREATED IN THE ONTARIO CANCER CLINICS, 1938-1958 INCLUSIVE

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THE Ontario Cancer Treatment and Research Foundation was incorporated in 1943 by a special act of the legislature of the Province of Ontario. The Cancer Act, which also reconstituted the Ontario Cancer Institute, states that "The object of the Foundation is to establish and conduct a programme of research, diagnosis and treatment in cancer, including ten categories involving research, service for and treatment of cancer patients." The act also provides for training of technical personnel and the provision and awarding of research fellowships.

Approximately 15 years ago, the former Medical Director of the Foundation, Dr. W. G. Cosbie, in consultation with other directors and Dr. A. H. Sellers, established regular clinical conferences. In the ensuing period there have been 16 separate clinical reviews, and they have been held annually for the past 13 years. The resultant reports probably represent the largest single retrospective studies of clinical material, by site in a restricted period.

The Twelfth Annual Clinical Conference was held at the University Center, University of Windsor, Windsor, Ontario, on November 5, 1965 with the general subject, "Cancer of the Ovary."

Nearly all of the radiotherapy administered in the Province of Ontario is given at the clinics of The Ontario Cancer Treatment and Research Foundation, or at the Ontario Cancer Institute. In the 21 year period, 1938 to 1958 inclusive, 1,983 patients with a clinical diagnosis of cancer of the ovary had been referred to the seven regional clinics of the Foundation or to the Ontario Cancer Institute, for consideration of radiotherapy. Selected for study were the records of 1,722 patients who received their initial radiotherapy at the clinics or were untreated anywhere.

Using the latest age specific incidence rates of ovarian cancer published by the Connecticut Tumor Registry for 1947 to 1951, it was estimated that, during the 21 year period, only 29 per cent of the cases with ovarian cancer available in the Province of Ontario had been referred to the clinics.[6] Many patients with strictly localized or borderline lesions, those in the oldest age groups and those with terminal disease, had apparently been excluded.

During the last 7 years of the period of study, the percentage of available cases referred for consideration of radiotherapy rose to 40 per cent. More of those with advanced disease were included. This latter period corresponds roughly to the general availability of cobalt 60 teletherapy in the clinics. Despite less favorable clinical material, the crude survival rate at 5 years has remained relatively unchanged.

At the fifth anniversary of the commencement of treatment anywhere, 25 per cent of the 1,722 review group patients were alive and apparently cancer-free. Three per cent were alive with cancer or with condition unknown. Sixty-seven per cent had died from ovarian cancer or unknown cause, 3 per cent from other causes, and 2 per cent were untraced. Of the 1,119 patients at risk

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for 10 years, 20 per cent were alive without cancer at the tenth anniversary, 74 per cent had died from ovarian cancer or other cause, and 4 per cent were untraced.

A diagnosis of malignancy was confirmed in 93 per cent of the cases.

For the purpose of this paper, discussion is limited to consideration of histologic classification and clinical staging, the relation of both to treatment method and survival and certain other factors influencing survival.

Several authors[2,4,9] have reported difficulty in the comparison of results between treatment centers because of lack of uniformity of histologic description and of clinical staging. The Cancer Committee of the International Federation of Gynaecology and Obstetrics have attempted to resolve the problem by proposals in both categories for the common primary epithelial tumors of the ovary.[4] An unsuccessful attempt was made to apply these suggestions retrospectively to the material in this conference. It was estimated that the histologic classification recommended by the International Federation of Gynaecology and Obstetrics would have excluded three-fourths of the diagnoses recorded in the several clinics for this study. An empirical classification closely corresponding to that of Novak, Novak and Woodruff[7,8] was chosen. This yielded 3 fairly homogeneous groups and 1 miscellaneous group: (1) Cystadenocarcinoma, 44.4 per cent; (2) solid carcinoma, 39.2 per cent (may include an unknown number of cystic tumors); (3) embryonic carcinoma, 7.6 per cent; and (4) other and unspecified, 8.8 per cent. We have grouped carcinomas occurring in dermoid cysts as teratocarcinoma, while Novak *et al.*[7,8] placed them with the cystic group.

CRUDE SURVIVAL RATES

HISTOLOGIC CLASSIFICATION

Patients with cystadenocarcinoma, yielding a crude 5 year survival rate of 37 per cent, or those having embryonic carcinoma, with a crude 5 year survival rate of 51 per cent, have done better than those with solid carcinoma (15 per cent) and those with miscellaneous tumors (20 per cent) (Fig. 1). If the tumor was cystic, patients with mucin-containing lesions had a higher survival rate (46 per cent) than those with serous cystic tumors (37 per cent), or cystadenocarcinoma not specified as mucinous or serous (33 per cent).

CLINICAL STAGING

A similar difficulty was encountered in attempting a uniform method of clinical staging (Fig. 2). Four clinical stages were used, classified as: I. localized to the ovary; II. limited extension beyond the ovary; III. metastases to other pelvic organs, ascites; and IV. metastases beyond these limits.

Rupture of a cyst in our study did not appear to affect the outlook adversely. These 4 stages had distinctive 5 year survival *rates* (66.2, 48.4, 19.5, and 5.9 per cent). Median survival *times* for the 4 stages were 60, 56.6, 14.4, and 7.3 months, respectively.

If Stages I and II are grouped and termed "early" cases, only 587 of our patients could be included. Their 5 year survival rate was 53.5 per cent. The remainder were classified as "late," comprising 1,070 cases, and had a 5 year survival rate of only 13.4 per cent. Thus approximately two-thirds of patients had reported late in their illness with a minimal chance for survival.

In general, the treatment of choice wherever practicable has been panhysterectomy (including bilateral salpingo-oophorectomy) followed by external radiotherapy. Some of the patients in this series received chemotherapy and some were treated with intraperitoneal radioactive gold, but groups of these two treatment modalities were too small for real statistical evaluation. Wherever complete surgical removal of all gross disease (including uterus and adnexa) was possible, the survival rate showed improvement and the likelihood of early and late recurrence was significantly lower than in

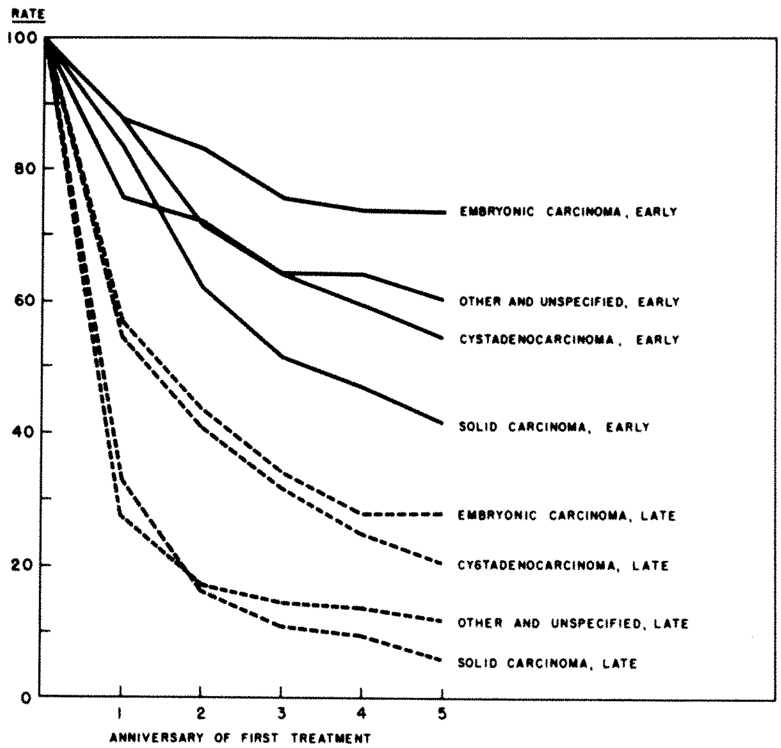

Fig. 1. Crude survival rates by histologic group and extent.

patients treated by incomplete surgical excision.

Several essayists in the course of the conference expressed the opinion that the 5 year survival rate was not increased if prophylactic postoperative radiotherapy was given following complete excision of the uterus and adnexa with cancer confined to one ovary (Stage 1).

DISCUSSION

In a small group of 33 patients included in this series treated by surgery alone, the 5 year crude survival rate was 66.7 per cent. For a similar small group of 28 patients with early disease included in the survey and treated by complete surgical excision followed by cobalt 60 beam therapy, there was an absolute survival rate of 57.9 per cent. This same experience has been reported by Holme[3] in England. For patients treated between 1936 and 1955 he recorded 5 year crude survival rates of 60 per cent for patients with early ovarian cancer treated by surgery alone and 52.6 per cent for those treated by surgery plus radiotherapy. On the other hand, patients with dysgerminoma, solid carcinoma and anaplastic serous cystadenocarcinoma, and those with incomplete removal of uterus or adnexa, have benefited from postoperative radiotherapy. Doses varying between 2,000 rads in 4 weeks administered as an abdominal bath for dysgerminoma, and 5,000 rads in 4 weeks to the pelvis to the level of the umbilicus for other cases, have been given.

In general, all other stages were treated by radiotherapy with the exception of those patients with terminal cancer. Some centers considered teratocarcinoma and mucinous carcinoma as totally radioresistant and have not treated these patients by radiotherapy. There has been disagreement as to the radioresponsiveness of most of the epithelial tumors.[1,5,10,11] Statistical analysis of our material has supported the impression that radiotherapy has added to the efficiency of surgical treatment among the late

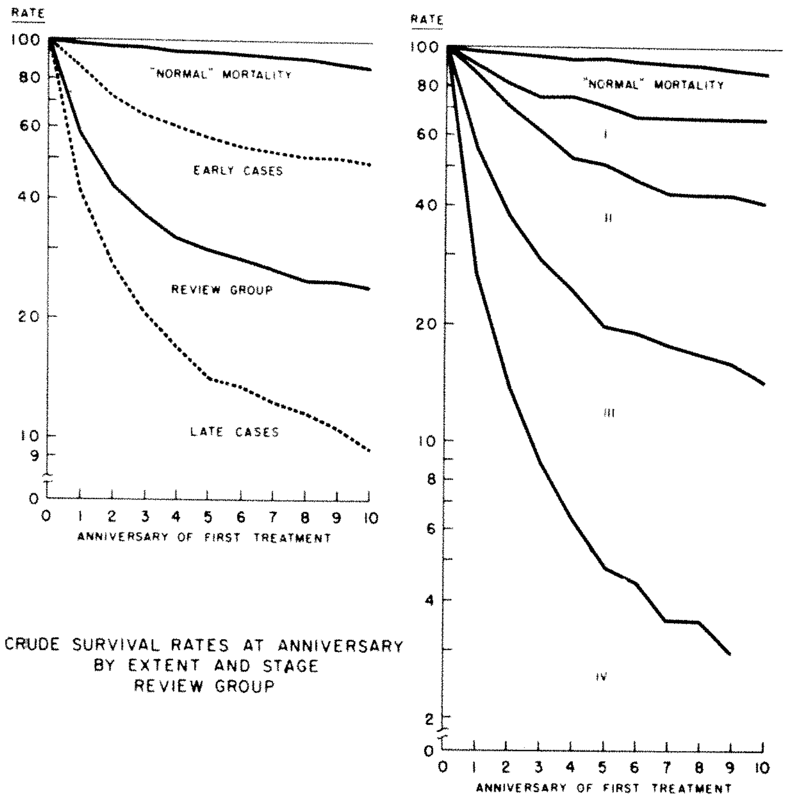

Fig. 2. Crude survival rates at anniversary by extent and stage (review group).

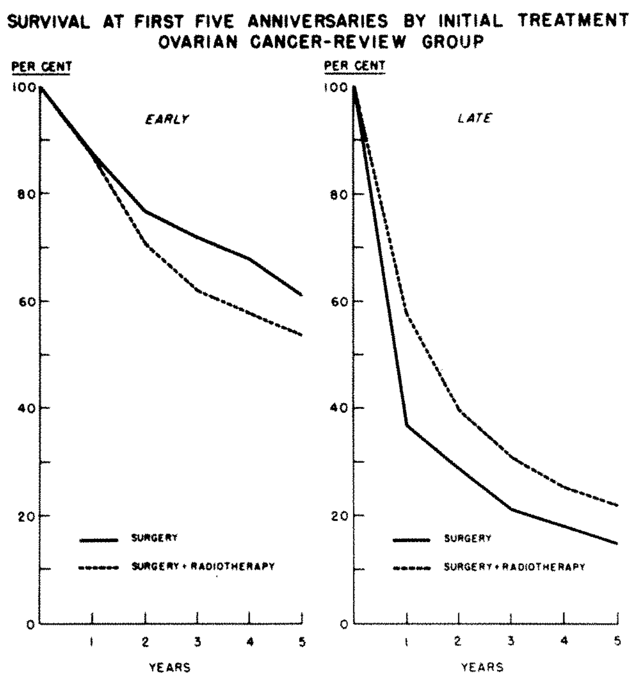

Fig. 3. Survival at first 5 anniversaries by initial treatment of ovarian cancer (review group).

cases. Survival rates at each of the first 5 anniversaries (Fig. 3) were higher after surgery with radiotherapy than after surgery alone.* For the late cases, the median survival time was 15 months following surgery with radiotherapy contrasted with 10 months following surgery alone. Sixteen per cent of late cases were recurrence-free for 5 years or more and only 6 per cent treated by surgery alone survived 5 years. In those patients treated by radiotherapy alone, the mean survival time was 6 to 7 months compared with the untreated group in which the survival time was 3 to 4 months.

SUMMARY

1. In the 21 year period 1938 to 1958 inclusive, 1,983 patients with a diagnosis of cancer of the ovary were registered with the 7 regional clinics of The Ontario Cancer Foundation and the Ontario Cancer Institute. Selected for study were 1,722 patients treated by radiotherapy or untreated anywhere.

2. Survival rates vary inversely with clinical staging and with the histologic type.

3. Radiotherapy has not increased the survival rate after complete surgical removal of Stage 1 cancer of the ovary over that obtained by surgery alone.

4. In all other stages the addition of radiotherapy has added to the efficiency of surgical treatment.

5. There is a need for a uniform system of reporting clinical stage and histologic type.

* Copies of the full proceedings are available at the office of The Ontario Cancer Treatment and Research Foundation, 69 Bloor Street East, Toronto 5, Ontario, Canada.

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TREATMENT OF LYMPHOMAS WITH MEDIUM KILOVOLTAGE EQUIPMENT AND INCIDENCE OF RECURRENCES*

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THE purpose of this paper is to review the experience and results of radiotherapy for lymphomas over an extended period of time and the incidence of recurrences. During the period reviewed (1946 to 1962) medium voltage therapy in the range of 250–280 kvp. was used with the dose varying up to a high of 4,000 r. Numerous papers have recently appeared in the medical literature regarding the treatment of lymphomas; however, most of these authors have had higher voltage equipment available.

MATERIAL

One hundred and sixty-seven patients were reviewed in this study and were categorized into the following: Hodgkin's disease—108 patients; lymphosarcoma—26 patients; reticulum cell sarcoma—23 patients; and giant follicular lymphoma—10 patients. All pathologic specimens were reviewed by the Armed Forces Institute of Pathology. Each of these disease groups was studied separately for the evaluation of survival and effects of therapy. Recurrences in previously irradiated sites were considered in the 108 patients with Hodgkin's disease in view of the initial tumor dose delivered.

The staging used in this study was essentially that outlined by Peters and Middlemiss,[11] that is:

Stage I Single site or one lymphatic region

Stage II Two or three contiguous lymphatic regions

Stage III Two or more distant lymphatic regions.

HODGKIN'S DISEASE

There were 108 patients who had a histologic diagnosis of Hodgkin's disease. In this group there were 45 patients with Stage I, 28 patients with Stage II, and 35 patients with Stage III disease. The age distribution is shown in Table I with a preponderance in the late teens and twenties, as would be expected in the age group seen in a military installation. The male:female breakdown was 84:24, while the male:female ratio for admissions during this same period of time was almost 50:50, attesting to the higher incidence in male patients.

The race distribution during the time studied revealed 105 Caucasians to 3 Negroes while the corresponding admissions to this hospital were 91 per cent Caucasian. In terms of survival there were 108 patients who were diagnosed 5 or more years ago and 39 who were diagnosed more than 10 years ago. The survival rate in the Stage I group was 30/45 or 67 per cent at 5 years and 14/22 or 64 per cent at 10 years. In the

Table I

AGE DISTRIBUTION IN HODGKIN'S DISEASE

Age (yr.)	Number of Patients
0–10	2
11–20	20
21–30	64
31–40	14
41–50	4
51–60	2
Over 60	2
Total	108

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Stage II group, the survival was 11/28 or 39 per cent at 5 years and 2/10 or 20 per cent at 10 years. In the Stage III group, the survival was 13/35 or 37 per cent at 5 years and 2/7 or 29 per cent at 10 years. The over-all survival rate for 5 years was 54/108 or 50 per cent and for 10 years was 18/34 or 46 per cent from the time of diagnosis (Table II). Survival was calculated on an absolute survival basis and patients lost to follow-up were considered deceased at the time of their last follow-up visit or later.

These patients were further reviewed as to the recurrences in sites previously treated. The purpose of this evaluation was primarily to relate the recurrences to the initial tumor dose utilizing medium kvp. therapy (250–280 kvp.). In determining a local recurrence, we adhered to the criterion that the patient survived more than 1 year after treatment in order to exclude those who showed local recurrences in addition to generalized disease. There were 34 local recurrences (Table III) in 26 patients, of whom 10 were still living at the time of this study. In this group of patients, 11 of the recurrences were within 1 year of the initial therapy, 8 were between 1 and 2 years, 5 between 2 and 3 years, 6 between 3 and 4 years, and 4 after 4 years. Of interest in this group was the fact that only 1 recurrence occurred when the initial dose was above 3,000 r.

LYMPHOSARCOMA

There were 26 patients with a diagnosis of lymphosarcoma, 25 of whom were treated 5 or more years prior to the undertaking of this study. There were 7/25 or 28 per cent still alive at the end of 5 years. There were 21 patients who were treated 10 or more years ago with 4 living beyond 10 years for 19 per cent 10 year survival. There were 17 Stage I, 2 Stage II, and 6 Stage III patients seen at the initiation of therapy. None of the Stage III patients lived beyond 5 years; however, 1 patient with Stage II lived beyond 10 years (Table IV).

RETICULUM CELL SARCOMA

There were 23 patients reviewed with the histologic diagnosis of reticulum cell sarcoma, 22 of whom were treated 5 or more years before the undertaking of this study with 3/22 or 13.6 per cent 5 year survival rate. There were 17 patients who were treated over 10 years ago; only 1 survived over 10 years to die of his disease at 12 years. At the time of this study none of the patients who were diagnosed as having reticulum cell sarcoma were alive. There were 15 patients with Stage I, 4 patients with Stage II, and 4 patients with Stage III. All 5 and 10 year survivals were from the Stage I group. The initial therapy on these patients varied from none in 3 patients to 4,000 r (Table IV).

GIANT FOLLICULAR LYMPHOMA

The last disease group to be considered is giant follicular lymphoma which comprised only 10 patients in this study (8 of whom were treated 5 or more years prior to our report): 6/8 or 75 per cent were living at the end of 5 years. There were 7 patients who were treated more than 10 years prior to the study of whom 4 are still living. In the Stage breakdown, there were 8 in Stage I, and 2 in Stage III with 1 of the Stage III patients still living at the end of 10 years (Table V).

Table II

SURVIVAL BY STAGE IN HODGKIN'S DISEASE*

Cases		Five Years		Ten Years	
Stage I	45	30/45	67%	14/22	64%
Stage II	28	11/28	39%	2/10	20%
Stage III	35	13/35	37%	2/7	29%
All Stages	108	54/108	50%	18/34	46%

* Represents absolute survival as 4 Stage II cases were lost to 5 year follow-up and 3 Stage I and 1 Stage III cases were lost to 10 year follow-up.

DISCUSSION

It is difficult to compare survival rates in most diseases due to the various types of staging for the same disease and the dependence upon the experience of the physi-

Table III

LOCAL RECURRENCE IN HODGKIN'S DISEASE

Case	Initials	Dose	Site	Time to Recurrence (mo.)	Final Outcome
1	C.D.	400	Right axilla	35	Living at 8+ years
2	W.F.	600	Left cervical	4	Dead at 3 years
3	W.B.	600	Right supraclavicular	30	Dead at 7+ years
4	E.S.	700	Right inguinal	24	Dead at 8+ years
5	E.S.	750	Mediastinum	37	Dead at 8+ years
6	R.D.	700	Right cervical	15	Dead at 3 years
7	W.H.	800	Left cervical	66	Dead at 10+ years
8	H.R.	800	Left cervical	27	Dead at 9+ years
9	T.F.	900	Mediastinum	28	Dead at 7+ years
10	E.M.	900	Right inguinal	5	Dead at 2+ years
11	C.D.	1,000	Right cervical	5	Living at 8+ years
12	B.D.	1,000	Left axilla	7	Living at 4+ years
13	H.R.	1,000	Liver and spleen	34	Dead at 9+ years
14	R.H.	1,200	Left cervical	57	Living at 12+ years
15	W.H.	1,200	Left inguinal	17	Dead at 10+ years
16	W.F.	1,200	Left cervical	7	Living at 12+ years
17	T.C.	1,250	Mediastinum	24	Dead at 3+ years
18	T.P.	1,250	Left axilla	3	Living at 6+ years
19	M.L.	1,300	Right cervical	22	Living at 2+ years
20	M.L.	1,000	Left cervical	11	Living at 2+ years
21	A.R.	1,400	Right cervical	40	Living at 7+ years
22	A.R.	1,400	Left cervical	14	Living at 2+ years
23	C.D.	1,550	Mediastinum	37	Living at 8+ years
24	J.M.	1,600	Left cervical	54	Dead at 11+ years
25	N.G.	1,600	Right cervical	11	Dead at 4+ years
26	D.K.	1,750	Right cervical	41	Living at 7+ years
27	P.J.	1,850	Right inguinal	12	Dead at 12+ years
28	A.B.	1,900	Right cervical	44	Living at 4+ years
29	S.B.	2,000	Right cervical	3	Dead at 3+ years
30	R.Y.	2,100	Right cervical	45	Living at 9+ years
31	M.G.	2,000	Mediastinum	3	Dead at 1+ years
32	T.P.	2,200	Right cervical	18	Living at 6+ years
33	J.S.	2,500	Mediastinum	15	Dead at 6+ years
34	L.R.	3,200	Mediastinum	54	Dead at 5+ years

cian who stages the patient. The latter is also true in the lymphomatous diseases; however, the staging technique outlined by Peters and Middlemiss,[11] due chiefly to its wide acceptance, has allowed a fair comparison to be made. In this paper the presence or absence of constitutional symptoms has not been included as a subdivision of Stage II due to incompleteness of the older clinical records.

Hodgkin's disease was first described by Hodgkin in 1832 and the roentgen ray treatment since 1902 has changed periodically until at the present time doses above 3,000 r are considered necessary for adequate therapy and prevention of recurrences. The chief difference of opinion among radiologists is the value of prophylactic treatment; however, a discussion of this point is not the purpose of this paper.

In comparing our results with others it is noted that the 5 year survival varies considerably, although the survival rate does decrease markedly once the patient has developed constitutional symptoms. The majority of the series reported stressed the

importance of megavoltage equipment for therapy, but in Hodgkin's disease and giant follicular lymphoma this is felt to be desirable although not necessary. In the treatment of lymphosarcoma and reticulum cell sarcoma, megavoltage therapy is felt to be necessary since with medium voltage therapy for the treatment of large areas, doses above 4,000 r are rarely obtainable.

In the Hodgkin's disease group the male and Caucasian preponderance reported by others was noted in this series, although the age and sex figures are weighted in a military installation which is necessarily selective; however, survival rates compare favorably with the reviewed studies. The fact that it is higher in many instances may be due to our lower age at the primary appearance of the disease.

In comparing our survival rates of the other lymphomatous diseases studied, a somewhat lower survival rate is noted as compared to those reported in the literature. Although we have separated our lymphosarcoma and reticulum cell sarcoma cases, we believe, as does del Regato,[8] that they are not separate entities and should be combined in statistical comparison. In the case of lymphosarcoma and reticulum cell sarcoma our combined over-all 5 year survival rate is 21.3 per cent as compared to 26.5 per cent as reported by Cook *et al.*[1] Scheer[14] reported on Stage I lymphomas and had a 75 per cent 5 year survival in lymphosarcoma and 60 per cent 5 year survival in reticulum cell sarcoma, while ours, when separated, reveals a 35.3 per cent and 21.4 per cent 5 year survival, respectively. The minimum dose required for the radical treatment of these lymphomas is 4,000 r and above, which is difficult to obtain with medium voltage equipment. In the patients evaluated in this study, the patients having lymphosarcoma and reticulum cell sarcoma showed a rather rapid progression toward generalized disease with only 2 patients surviving more than 1 year after the local recurrence, one in each group.

In giant follicular lymphoma our 5 year over-all survival rate was 75 per cent which is somewhat higher than that reported by Cook *et al.*,[1] and the others quoted in his paper; however, our series is too small for comparison. In our series 2 patients with tumor doses as low as 1,000 r did not demonstrate local recurrences until 1 and 13 years following the initial therapy.

Table IV

SURVIVAL BY STAGE IN LYMPHOSARCOMA AND RETICULUM CELL SARCOMA

Cases		Five Years	Ten Years
		Lymphosarcoma	
Stage I	17	6/17 (35.3%)	3/14 (21.4%)
Stage II	2	1/2 (50.0%)	1/2 (50.0%)
Stage III	7	0/6 (0.0%)	0/5 (0.0%)
All Stages	26*	7/25 (28.0%)	4/21 (19.0%)
		Reticulum Cell Sarcoma	
Stage I	15	3/14 (21.4%)	1/11 (9.1%)
Stage II	4	0/4 (0.0%)	0/2 (0.0%)
Stage III	4	0/4 (0.0%)	0/4 (0.0%)
All Stages	23†	3/22 (13.6%)	1/17 (5.9%)
		Lymphosarcoma and Reticulum Cell Sarcoma	
All Stages	49	10/47 (21.3%)	5/38 (13.2%)

* 25 patients were treated 5 or more years prior to this report.
† 22 patients were treated 5 or more years prior to this report.

Table V

SURVIVAL BY STAGE IN GIANT FOLLICULAR LYMPHOMA

Cases		Five Years	Ten Years
Stage I	8	5/7 (71.4%)	3/6 (50.0%)
Stage II	0	0	0
Stage III	2	1/1 (100.0%)	1/1 (100.0%)
All Stages	10*	6/8 (75.0%)	4/7 (57.1%)

* 8 patients were treated 5 or more years prior to this report.

SUMMARY

1. In spite of the variable dose initially used in the treatment of Hodgkin's disease, the long term survival is in the general range as compared to institutions where the initial tumor dose is above 2,500 r; however, the problem of local recurrences and subsequent retreatment to local sites re-

mains a problem in cases where the initial tumor dose is below 3,000 r.

2. The response of lymphosarcoma, reticulum cell sarcoma and giant follicular lymphoma, as treated at this institution, does not indicate a homogeneous group as reported from other institutions. Only the giant follicular lymphoma appears to hold a satisfactory survival rate when treated by means of medium voltage therapy.

3. On the basis of our material, it would appear that an effort should be made to have patients with lymphosarcoma and reticulum cell sarcoma treated at institutions where supervoltage or cobalt 60 therapy is available.

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A STUDY OF SURVIVAL IN 279 CASES OF HODGKIN'S DISEASE*

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IN SPITE of overwhelming evidence to the contrary, the myth of the universal fatality of Hodgkin's disease continues to be propagated. Easson[2] calls this "the pernicious policy of pessimism, pills, and procrastination." Analysis of the results of treatment of the series of patients treated at Walter Reed General Hospital clearly illustrates the positive impact of therapy on survival and is an effective argument for optimism and vigorous therapy. It is the purpose of this communication to document this experience, to compare it with that of other investigators, to emphasize the parameters of therapy which need further clarification, and to indicate how this may be accomplished to further improve the already significant survival in this disease.

CLINICAL MATERIAL

In 1955 Healy *et al.*[3] reported the experience at Walter Reed General Hospital from 1938 to 1949 in treating 219 cases of Hodgkin's disease primarily with roentgen rays. It was not until 1949 that a functional tumor registry began operation and unfortunately the records of this earlier study group could not be made available for inclusion in the present report. Since 1949, 400 additional patients have been treated; 279 have been at risk for 5 years and 170 for 10 years. Twenty patients were lost to follow-up and 6 patients died of intercurrent disease. All but 2 of these 26 patients were considered dead from Hodgkin's disease. These 2 patients who died 10 or more years after treatment of unrelated causes, had no evidence of Hodgkin's disease at autopsy, and were considered as survivors. All cases were staged retrospectively by the criteria given in Table I,A. The distribution of patients according to stage is shown in Table II along with similar tabulation from 2 other well-known series. The diagnosis was established by tissue biopsy in every case and the slides were interpreted or reviewed by the Walter Reed General Hospital pathology service. Reed-Sternberg cells were identified in all cases and were considered the *sine qua non* for the diagnosis.

In general, the earlier cases were treated primarily by radiation. In Stage I and II, tissue doses varied from 2,400 to 2,800 r in 2 to 4 weeks. Orthovoltage radiation (200 kvp., 20 ma., half value layer 1.02 mm. Cu, 50 cm. target skin distance) was used for lesions in the neck, axillae, and groin, whereas supervoltage radiation (1,000 kvp., 3 ma., half value layer 3.6 mm. Pb, 70 cm. target skin distance) was used preferentially for the mediastinum and abdomen. In Stage III cases the doses of radiation were quite variable but were mostly of the order of 2,500 r in 2 to 4 weeks to involved areas. There was no firm policy to determine whether orthovoltage or supervoltage radiation would be used. Chemotherapy and steroids were given alone or with irradiation in various schedules, generally in the more advanced cases, whether primary or recurrent.

RESULTS

The results of treatment are summarized in Tables III, IV and V. When comparing the results of treatment in different institutions, a number of variables can make comparison of numbers representing per cent

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TABLE I

STAGING OF HODGKIN'S DISEASE

A. Staging according to Kaplan[4] (1966)		B. Staging according to Peters and Middlemiss[7] (1958)	
Stage I	Single abnormal lymph node	Stage I	Disease limited to a single site or lymphatic region
Stage II	Two or more discrete abnormal lymph nodes, limited to one side of the diaphragm	Stage II	Disease involves two or three proximal lymphatic regions A Without symptoms of systemic disease B With symptoms of systemic disease
Stage III	Disease on both sides of the diaphragm but limited to lymph nodes, spleen, or Waldeyer's ring	Stage III	Disease involving two or more distant lymphatic regions
Stage IV	Involvement of bone, bone marrow, lung parenchyma, pleura, liver, skin, gastrointestinal tract, central nervous system Kidney or sites other than lymph nodes, spleen or Waldeyer's ring		

All stages are subclassified as A or B to describe absence or presence of systemic symptoms, respectively.

survival quite misleading. When total over-all survival is the same but is considerably different in the various stages, one may assume that different criteria have been used for staging and/or that the number of patients in the various stages comprise a different proportion of the total number in the compared series. Both factors are involved in the present comparison. The staging criteria used by Peters *et al.*[8] and Lukes *et al.*[5] were more selective in Stage II (Table I,B). By removing the word proximal (interpreted to mean "in proximity to") from the description of involved areas, a number of patients who formerly were assigned to Stage III can be classified as Stage II. This may in part account for the larger fraction of Stage II patients in the Walter Reed General Hospital series. The smaller proportion of Stage III patients in both the series of Lukes *et al.*[5] and our series undoubtedly reflects the younger age group at risk in the Army environment. Stage III patients in the series of Peters *et al.*[8] comprise the older age groups. In Stage III, it is apparent that survival is poor in all series.

The strange phenomenon in the series of Peters *et al.*,[8] whereby better survival is

TABLE II

DISTRIBUTION OF CASES BY STAGE

Stage	Peters *et al.*[8] (per cent)	Lukes *et al.*[5] (per cent)	Walter Reed General Hospital (per cent)
I	22	38	25
II	36	34	45
A	16	15	31
B	20	19	14
III	42	28	24
IV			6

TABLE III

ABSOLUTE 5 YEAR SURVIVAL

(per cent)

Stage	All	Male	Female
I	55	53.6	60
II	47.9	44.9	53.3
A	55.3	50.0	64.5
B	31.6	33.3	28.6
III	15.4	17.9	0
A	11.1	13.3	0
B	17.0	19.5	0
IV	20.0	9.1	50
A	33.3	0	100
B	11.1	14.3	0
All patients	40.8 (279)	38.0 (203)	48.8 (76)

ANGIOCARDIOGRAPHY IN DIAGNOSIS OF PERICARDIAL EFFUSION AND PULMONARY STENOSIS IN HODGKIN'S DISEASE*

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IN HODGKIN'S disease, angiocardiography, by outlining the cardiovascular system, permits a better appreciation of the ravages of the disease in the mediastinum and hilus, establishes the diagnosis of pericardial effusion, and when present, reveals extrinsic pulmonary stenosis. The 3 patients, herein reported, are unusual in that they had both massive mediastinal and hilar lymphadenopathies and enlarged cardiac silhouettes due to pericardial effusion. In addition, in the first patient (Case 1), a systolic murmur was heard over the pulmonic area which was shown by angiocardiography to be caused by pulmonary stenosis due to a mediastinal tumor. He, as well as the second patient with a sarcomatous type of Hodgkin's disease, developed pericardial effusion after becoming refractory to radiation and chemotherapy. This proved to be ominous; death ensued in a few months. In the third case, the pericardial effusion and hilar and mediastinal lymphadenopathies were initial findings of the disease and because of these, the diagnosis of lymphoma was suggested; scalene biopsy confirmed it, and radiation therapy effected a long remission. Angiocardiography was especially valuable in the diagnosis of pericardial effusion, demonstration of the extent of the mediastinal and hilar disease, and visualization of the pulmonary stenosis.

REPORT OF CASES

Case 1. *Refractory mediastinal and hilar lymphadenopathy, pulmonary stenosis, and pericardial effusion due to Hodgkin's disease.* A 33 year old physician (N.Y.H. No. 968448) was referred for angiocardiography by Dr. Allyn B. Ley on February 11, 1964. Seven years earlier, a roentgenogram of the chest had been made because of pleurisy and it showed a mediastinal tumor. Right thoracotomy and biopsy of the mass disclosed Hodgkin's disease. He was then treated with radiation therapy (250 kv., anteroposterior ports, total dosage 2,400 r) to the mediastinum. He remained well until May 1961, when on re-examination he complained of a persistent cough, and a roentgenogram of the chest again revealed mediastinal masses; other lymph node and retroperitoneal masses were not found. Supervoltage treatment to the mediastinum was prescribed, and he improved. In January 1962, he had fever (100°F.) and although he felt well, a small (1–2 cm.) left supraclavicular lymph node was palpated. A roentgenogram of the chest again showed widening of the mediastinum. A third course of radiation therapy using rotational technique was begun. He improved, the fever and mediastinal masses disappeared, and he remained well until January 1963, when he again complained of cough and feverishness, and examination showed enlarged lymph nodes in the right supraclavicular fossa and the reappearance of mediastinal masses. Biopsy of a right-sided supraclavicular lymph node again showed Hodgkin's disease. Chemotherapy (vinblastine [10 mg. weekly] and chlorambucil [4 mg. daily]) were begun in combination with varying rest periods, and again he improved. Beginning in July 1963, the roentgenograms of the chest showed reappearance of widening of the mediastinum. Radiation therapy was added to the treatment in December 1963.

The patient then began having malaise, intermittent fever, cough and dyspnea. A roentgenogram of the chest showed enlargement of the cardiac silhouette and of the mediastinum (Fig. 1, *A* and *B*). Enlarged

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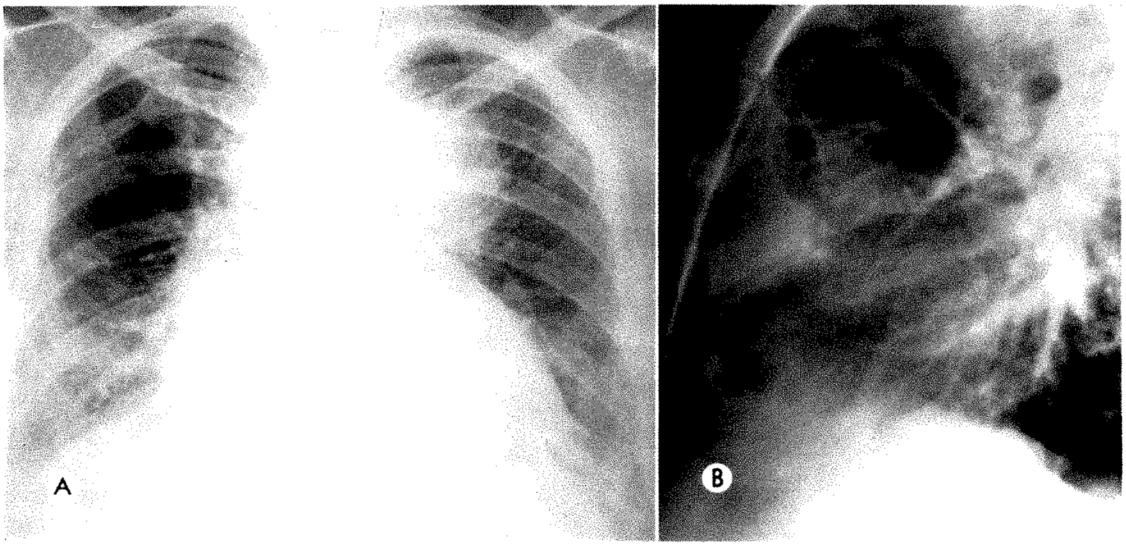

Fig. 1. Case I. (*A*) Frontal teleroentgenogram of the chest showing enlarged mediastinal and hilar masses (especially on the left side) and enlargement of the cardiac silhouette. The deformed fourth posterior right rib is due to exploratory thoracotomy made 7 years earlier. (*B*) Lateral roentgenogram of the chest showing filling of the entire retrosternal space.

lymph nodes in the supraclavicular fossa and left axilla were found, and the spleen was palpable. There was also a systolic (Grade 3) murmur along the left border of the sternum radiating to the neck and precordium. Radiation therapy (betatron, 12×10 cm. port) over the anterior mediastinum was added to the chemotherapy. Angiocardiography showed narrowing of the left innominate vein, a huge pericardial effusion, stenosis of the pulmonary artery at its bifurcation, and narrowing of the right and left pulmonary arteries by the mediastinal masses (Fig. 1, *C–G*).

Following a sixth course of radiation treatments (betatron, 12×10 cm. ports, total dosage 1,300 r), he again improved; the pulmonary systolic murmur diminished to Grade 1, and he remained well until May 1964, when he began having dyspnea, ankle edema, cough, and fever. He was treated with methylhydrazine and was somewhat improved, but then he developed sinusitis, purpura over the legs, and pretibial edema. He continued to do poorly and died at home on July 4, 1964. A postmortem study was not obtained.

Case II. *Intractable pericardial effusion and hilar and mediastinal enlargement in Hodgkin's disease with sarcomatous features.* A 21 year old man (N.Y.H. No. 977592), referred by Dr. William Geller, had had a biopsy of a neck lymph node in December 1963, that showed Hodgkin's disease with sarcomatous features. He did not respond to vinblastine, HN_2, and methylhydrazine derivative. Response to radiation therapy was also poor and transient. On May 5, 1964, he was referred for angiocardiography because of increasing hilar and cardiac silhouette shadows (Fig. 2*A*). Angiocardiography disclosed a huge pericardial effusion (Fig. 2, *B* and *C*). He died on August 15, 1964, and postmortem study confirmed the diagnosis of pericardial effusion. The lungs showed radiation changes of the exudative type with superimposed acute bronchopneumonia. Both axillae contained huge lymph nodes which had invaded the chest wall and intercostal muscles. The carinal, hilar, paratracheal, peripancreatic, and para-aortic lymph nodes were markedly enlarged.

Case III. *Pericardial effusion and hilar and mediastinal lymphadenopathy in Hodgkin's disease amenable to treatment.* A 55 year old woman (N.Y.H. No. 999979) was referred for angiocardiography on January 7, 1965, because of hilar and cardiac enlargement (Fig. 3, *A* and *B*). Angiocardiography showed a moderate pericardial effusion and a large, 7×7 cm. mass adjacent to the aorta, which was located be-

TABLE I

ACQUIRED PULMONIC STENOSIS DUE TO MEDIASTINAL TUMORS

	Year	Author	Age	Sex	Pathology	Complaints	Cardiac Murmurs	Angiocardiogram and Gradient mm. Hg*	Follow-up
1.	1944	Rusby[12]	25	F	Teratoma adherent to pericardium	Chest pain, dyspnea and cough	Systolic bruit second left interspace		Tumor partially excised; well 6 years after operation
2.	1948	Maier[8]	4	F	Teratoma adherent to pericardium	Dyspnea and fatigue	Harsh systolic murmur over entire precordium		Tumor completely removed; well 3½ years after operation
3.	1955	Fry *et al.*[6]	23	M	Malignant teratoma involving pericardium	Chest pain and fatigue	Harsh systolic murmur and thrill	Inconclusive	Thrill and murmur disappeared after excision of tumor but re-occurred in 1½ months; died within 4 months
4.	1956	Wood[23]			Lymphatic cyst		Pulmonic systolic murmur and thrill	Tumor compressed pulmonary artery; gradient 52	Tumor resected; murmur disappeared
5.	1957	Waldhausen *et al.*[19]	23	M	Primary intrapericardial mesothelioma	Chest pain and cough	Systolic murmur (Grade 3/6) left second interspace widely transmitted	Selective right ventriculogram showed pulmonic stenosis; gradient 10	Tumor excised; cardiac murmur disappeared, and prophylactic irradiation given to mediastinum postoperatively
6.	1958	Winter[21]	21	M	Hodgkin's disease	Chest pain and dyspnea	Harsh systolic murmur (Grade 2) with increased intensity in left infraclavicular area	Unsatisfactory; gradient 20	Tumor excised, given irradiation postoperatively; murmur vanished
7.	1962	Babcock *et al.*[1]	15	F	Lymphoma	Asymptomatic	Harsh systolic ejection murmur (Grade 4/6) over pulmonic area and widely transmitted	Selective right ventriculogram showed infundibular stenosis; gradient 25	Spleen enlarged, supraclavicular biopsy positive, treated successfully with nitrogen mustard; tumor and murmur disappeared
8.	1965	Shaver *et al.*[13]	27	F	Hodgkin's disease of thymus	Vague precordial discomfort	Systolic ejection murmur (Grade 2/3) in second and third intercostal spaces along left border of sternum	Selective left ventriculogram failed to show effect of tumor on pulmonary artery; gradient 10	Tumor excised, radiation therapy not given, murmurs disappeared; postoperative cardiac catheterization normal
9.	1966	del Castillo *et al.*[3]	51	F	Chondrosarcoma of sternum	Sudden onset of sharp midsternal pain radiating to interscapular area and both shoulders	Blowing systolic (Grade 2/4) murmur second left intercostal space adjacent to sternum	Stenosis outflow tract right ventricle	Tumor and adjacent cartilages excised and closed with stainless steel mesh; murmur disappeared
10.	1967	Case 1	33	M	Hodgkin's disease in terminal stage	Malaise, intermittent fever, cough and dyspnea	Systolic murmur (Grade 3) along left border of sternum radiating to neck and precordium	Pulmonic stenosis and pericardial effusion (Fig. 1, *D* and *E*)	Murmur decreased following irradiation and chemotherapy but returned terminally

* Right ventricle/pulmonary artery.

SUMMARY AND CONCLUSIONS

Angiocardiography, by opacifying the cardiovascular structures, permitted the diagnosis of pericardial effusions and outlined the greater extent of mediastinal masses in 3 patients with Hodgkin's disease with mediastinal and hilar lymphadenopathies, and enlargement of the cardiac silhouette. In 2 of the cases, pericarditis was a late complication of Hodgkin's disease that had become refractive to radiation and chermotherapy, and the pericarditis proved to be of ominous diagnostic significance; death occurred 5 and 9 months, respectively, following development of pericarditis. In contrast, a remission of the disease with disappearance of the hilar and mediastinal lymphadenopathies and of the pericardial effusion resulted following treatment of the third patient who had a pericardial effusion at the onset of the disease. Pulmonic stenosis due to compression of the pulmonary artery by Hodgkin's disease occurred terminally in 1 patient, and was demonstrated by angiocardiography.

Angiocardiography is recommended for

the diagnosis of great vessel and pericardial complications of mediastinal and hilar Hodgkin's disease, and *vice versa*. Whenever there is mediastinal and hilar lymphadenopathy, enlargement of the cardiac silhouette, and/or great vessel stenosis or occlusion, Hodgkin's disease should be considered in the differential diagnosis.

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MALIGNANT DISEASE OF THE PARANASAL SINUSES AND NASAL CAVITY*

IMPORTANCE OF PRECISE LOCALIZATION OF EXTENT OF DISEASE

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BECAUSE of the proximity of such vital structures as the eyes and brain and complex anatomic relationships of the areas involved, cancers of the paranasal sinuses and nasal cavity require greater than usual precision in localization of the disease. The skill with which this localization is performed is a major factor in determining both survival and the incidence of complications. It is characteristic for these tumors to progress to an advanced stage while remaining localized with infrequent lymph node or distant metastases.[26] The local recurrence rate (36 per cent in this series), therefore, underscores the frequent failure to achieve and maintain local control of these neoplasms[22] despite the combined use of radiotherapy and surgery in many cases.[10,13,17]

Whether the tumor originates in the nasal cavity or in one of the sinuses, spread to surrounding structures is the rule by the time the patient presents for treatment.[20,21] Identification of the specific site of origin can be difficult or impossible when the disease is advanced.[25] The roentgenographic examination is the most accurate clinical technique for establishing the origin and routes of spread of these lesions.[3,12,15] In order to secure the maximum information as to the extent of these neoplasms, we have obtained roentgenograms in the following views:[3,7]

(1) Caldwell's, Waters's, and lateral views of the paranasal sinuses using the Potter-Bucky diaphragm and small cones.

(2) Two submentovertical views, the second view being obtained with increased cephalic angulation of the tube to displace the image of the mandible anteriorly and to avoid superimposition of the posterolateral wall of the maxillary sinus and orbital surface of the greater sphenoid wing.

(3) Frontal tomograms at 1 cm. intervals from 2 to at least 9 cm. from the tabletop with the patient prone and the canthomeatal line perpendicular to the table.

(4) Lateral and transverse tomograms, and, in selected cases, positive contrast studies of the sinuses[8] and of the nasopharynx[14] are of value.

The tomograms are especially useful in realizing a three-dimensional concept of the extent of disease;[16,24] also, bone erosion is more easily detected in the absence of superimposed obscuring densities.[7] Although roentgenographic identification of bone erosion is not pathognomonic of malignant disease, its discovery requires intensive investigation to determine its cause, which, in most cases, will prove to be cancer.

SITES OF ORIGIN AND ROUTES OF SPREAD

A number of systems of classification of antral carcinomas have been advanced.[5,19,23] We have followed Baclesse[1] in dividing

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antral lesions according to sites of origin as determined by roentgenographic studies.

Certain patterns of disease extension characterize malignant disease arising in these different sites:[2,3]

(1) *Maxillary sinus.*

A. Infrastructure, below the level of the inferior surface of the middle turbinate (Fig. 1, *A* and *B*). Tumors arising here can be confused with those originating in the upper gum as they may extend into the hard palate, alveolar process or gingivobuccal sulcus and be seen during the examination of the mouth. Extension may also occur into the soft tissues of the cheek below the zygoma, nasal cavity, and in rare instances into the pterygoid plates and pterygopalatine space.

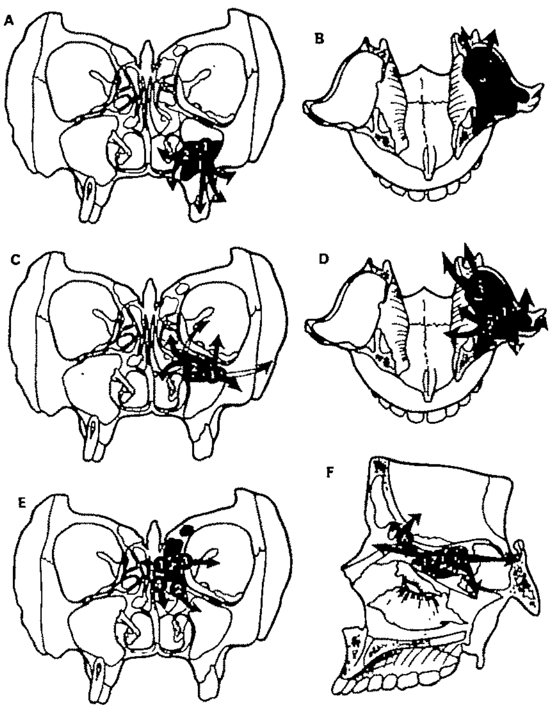

Fig. 1. Routes of spread of paranasal sinus carcinomas.

(*A* and *B*) Antral infrastructure origin: (1) Into the alveolar process, gingivobuccal sulcus and soft tissues of the cheek below the zygoma; (2) into the nasal cavity and hard palate; (3) into the pterygoid plates and pterygopalatine space.

(*C* and *D*) Antral suprastructure origin: (1) into the zygoma, posterolaterally into the infratemporal fossa, and into the orbit; (2) into the nasal cavity, ethmoid sinuses and orbit; (3) into the pterygopalatine space and base of skull. This occurs more commonly than it does in infrastructure lesions.

(*E* and *F*) Ethmoid sinus origin: (1) Into contralateral ethmoid sinuses; (2) into the antrum with erosion of the ethmoidomaxillary plate; (3) into the orbit; (4) into the nasal cavity with invasion of the septum and turbinates; (5) into the sphenoid sinus, nasopharynx and base of the skull; (6) into the frontal sinus, cribriform plate and anterior cranial fossa; (7) forward into the frontonasal angle.

B. Suprastructure, above the level of the inferior surface of the middle turbinate (Fig. 1, *C* and *D*). These tumors frequently extend superiorly and medially into the orbit, ethmoid sinuses, and nose; laterally into the zygoma and posterolaterally into the infratemporal fossa; and posteriorly into the pterygopalatine space and base of skull.

C. Additional specific sites:

(a) Ethmoidomaxillary. This site contains a highly malignant group originating in the region of the ethmoidomaxillary plate which separates the ethmoid region from the superomedial portion of the antrum. The tumors involve the antrum and ethmoid from the onset and extend rapidly through the medial wall of the orbit and medial portion of the orbital floor.

(b) Endosinus. These tumors spread diffusely within the mucosal lining of the antrum without bone erosion initially when the tumor breaks through the bony walls; spread occurs virtually simultaneously in all directions.

(c) Medial wall. Tumors originating in the medial or nasal-antral wall mimic primary nasal tumors in their routes of spread.

(2) *Ethmoid sinuses* (Fig. 1, *E* and *F*). Neoplasms may originate in the anterior, middle, or posterior sinuses, but

extension throughout the ethmoid region on the side of involvement is usually present when the patient is first seen. Because of the central location of the ethmoid sinuses, extension of tumor often involves all of the other paranasal sinuses as well as the orbit, nasal cavity, nasopharynx, and base of skull.

(3) *Frontal sinus* (Fig. 2*A*). Primary carcinomas of the frontal sinuses as well as those of the sphenoid sinuses are quite rare.[11] It is often difficult to distinguish frontal neoplasms from tumors of the ethmoid sinuses spreading upward. Frontal neoplasms may extend anteriorly into the forehead, often with secondary infection, inferiorly into the ethmoid sinuses and into the orbit, and posteriorly into the dura and frontal lobes.

(4) *Sphenoid sinuses* (Fig. 2*B*). The tumors arising in the sphenoid sinus and extending inferiorly into the nasopharynx are difficult to differentiate from primary nasopharyngeal cancer spreading superiorly. Extension may also occur through the floor of the middle cranial fossa and sella turcica as well as anteriorly into the posterior ethmoid cells and nasal cavity.

(5) *Nasal cavity*. There are three anatomic regions:
   A. The vestibule is the expanded lower portion of the nasal cavity just inside the external nares. Tumors arising here are essentially skin cancers and not considered in this report.
   B. Nasal cavity proper.
   C. The olfactory region, a narrow strip in the apex of the nasal cavity extending a short distance onto the medial and lateral walls.

For purposes of classification, the tumors of the nasal cavity have been divided into two groups:

(1) A *superior* group which arises above the horizontal plane lying at the level of the lower border of the superior turbinate (Fig. 2, *C* and *D*). Because part of the lymphatic drainage in this region passes through the cribriform plate and unites with the lymphatics of the subarachnoid space,[18] tumors in this region may extend rather quickly to the anterior cranial fossa. Early extension also often occurs to the ethmoidal region, orbit, and superior medial antrum. Contralateral spread is less common than with ethmoidal tumors.

(2) An *inferior* group (Fig. 2, *C* and *D*) arises in the lateral wall (nasal antral septum), middle and inferior

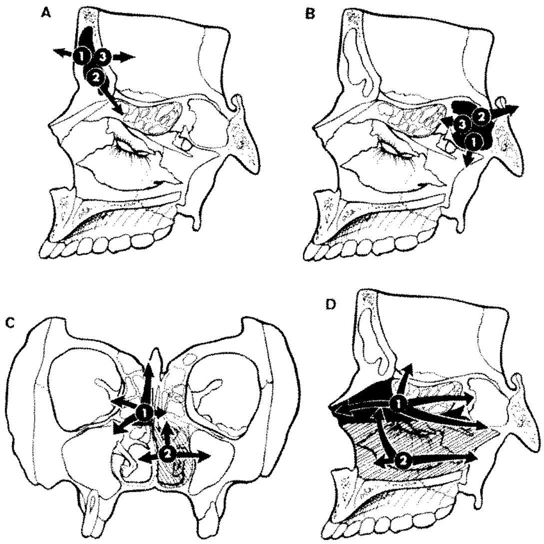

Fig. 2. Routes of spread of paranasal sinus and nasal carcinomas.

(*A*) Frontal sinus origin: (1) Anteriorly producing mass in the region of the bregma and nasion, often with secondary infection; (2) into the ethmoid sinuses and through the superior medial wall of the orbit; (3) into the dura and frontal lobes.

(*B*) Sphenoid sinus origin: (1) Into the nasopharynx; (2) through the floor of the middle cranial fossa and sella turcica; (3) into the posterior ethmoid cells and nasal cavity.

(*C* and *D*) Nasal cavity origin: (1) Into the anterior cranial fossa, ethmoid cells, orbit, antrum and commonly posteriorly into the sphenoid sinus and along the base of the skull and roof of the nasopharynx; (2) posteriorly to protrude through the posterior choana, superiorly into the upper nasal cavity and occasionally to the other side of the nose.

TABLE I

PARANASAL SINUSES—NASAL CAVITY
(1954–1963)
HISTOLOGY

	No. of Patients	Per Cent
Squamous cell carcinoma	79	65
Unclassified malignancies	17	14
Adenocarcinoma	8	7
Rhabdomyosarcoma	7	6
Fibrosarcoma	3	2.5
Esthesioneuroepithelioma	3	2.5
Miscellaneous	4	3
Total	121	100

turbinates or nasal septum. These tumors frequently extend posteriorly to protrude through the posterior choana into the nasopharynx where they may be seen by mirror examination or demonstrated by positive contrast nasopharyngography.

CASE MATERIAL

The charts and roentgenograms of 121 patients with previously untreated primary malignant disease of the paranasal sinuses and nasal cavity seen at the University of Texas M. D. Anderson Hospital and Tumor Institute at Houston from 1954 through 1963 have been analyzed. Nearly two-thirds of the lesions were squamous cell carcinomas (Table I). In 58 per cent of cases, the lesions arose in the maxillary sinus (Table II). Of these, 37 per cent originated in the infrastructure, 14 per cent in the suprastructure, and 6 per cent were ethmoidomaxillary; the remainder were so extensive that their site of origin could only be designated as the maxillary sinus. Nasal cavity and ethmoid lesions followed in that order of frequency.

Nearly equal numbers of patients were treated by surgical procedures alone, radiation therapy alone, or combined surgical and radiation therapy with the irradiation given either preoperatively or postoperatively. In general, surgical therapy was selected for patients with relatively localized disease, while combined surgical and radiation therapy was used for the more advanced lesions. Radiation therapy as the sole method of treatment was used prin-

TABLE II

PARANASAL SINUSES—NASAL CAVITY
(1954–1963)
RECURRENCES AND 5 YEAR SURVIVAL BY SITE OF ORIGIN

Origin	No. of Patients			Per Cent Recurrences	Per Cent 5 Year Survival*	
					Absolute	Determinate†
Antrum						
Infrastructure	26			15	66.7	66.7
Suprastructure	10			40	50	50
Ethmoidomaxillary	4			(50)	(0)	(0)
Massive	30			57	25.9	33.3
Over-all antrum		70		39	35.1	41.9
Ethmoid	20			45	50	50
Frontal	1			(100)	(0)	(0)
Sphenoid	2	23		(50)	(50)	(50)
Total sinuses			93	40.8	35.1	39.6
Nasal cavity			28	21.4	63.2	75
Total Series			121	36.3	42.5	48.4

* Not all cases are included in the analysis of 5 year survival; in some, an insufficient time has elapsed following treatment.
† For determinate survival, patients dying of intercurrent illnesses or lost to follow-up are excluded.

cipally for nasal cavity lesions, advanced sinus cancer treated for palliation only, and when the patient refused operation or was medically inoperable.

TREATMENT PLANNING

The paranasal sinuses and nasal cavity compose an anatomic area where the sophisticated wedge filter technique is especially useful.[6,9] It has proved helpful in preparing, from the patient's contour, a cardboard cutout with leveling device attached, to insure reproducible positioning.[9]

Because of the rounded contour of the cheek, a right angle pair of wedge filtered portals may seem to be optimal but this is rarely, if ever, used because the opposite eye is in the treatment field. Furthermore, in practice, overlapping or missing is not easy to avoid at the junction of portals at right angle (Fig. 3*A*). A dose distribution which is superior in several respects may be achieved by posterior angulation of the lateral field (Fig. 3*B*). This reduces the dose to the contralateral eye and also raises the dose posteromedially in the region of the pterygopalatine space. Care must be taken to be sure that the angulated field extends posteriorly far enough to encompass lateral disease.

For tumors originating and extending largely in the midline (ethmoid, frontal,

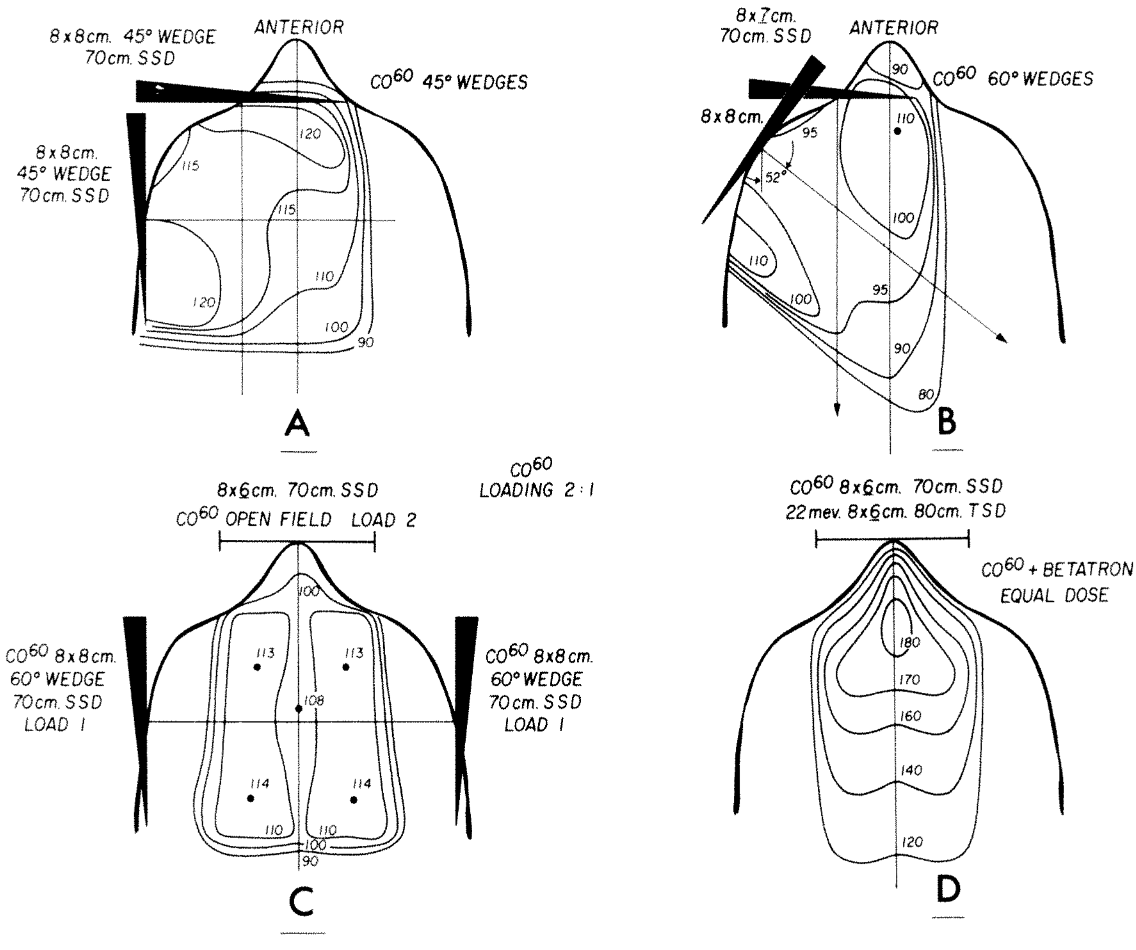

Fig. 3. (*A–D*) Various patterns of isodose distribution available for treatment of patients with nasal and paranasal sinus malignancies. For a description, see text. (From G. H. Fletcher, Textbook of Radiotherapy, Lea and Febiger, Philadelphia, 1966.)

sphenoid, nasal) an anterior open field is used. The anterior field may be L-shaped if disease has extended into a maxillary sinus. Addition of a pair of lateral wedge filtered portals yields an homogeneous dose pattern extending posteriorly as far as required (Fig. 3*C*). If disease extends far anteriorly, 6,000 rads are given through an anterior portal with dose build-up posteriorly with wedged lateral portals. Often the anterior field can be reduced near the conclusion of treatment and the additional radiation given as a "boost." High energy electrons, because of their limited depth of penetration, may be used to advantage for a portion of the anterior radiation and may be tailored to spare the underlying frontal lobes and brain stem.

In some instances, a combination of 22 mev. and cobalt 60 irradiation to an anterior field may give a satisfactory dose distribution (Fig. 3*D*).

Tumor doses are in the range of 5,000 rads in 5 weeks preoperatively, or 6,000 rads in 5 to 6 weeks postoperatively or when irradiation is used alone. An additional 500 to 1,000 rads may be given through reduced fields to sites of possible residual disease.

When orbital involvement has not been demonstrated, it is tempting to avoid irradiation of the ipsilateral eye, but this may lead to inadequate irradiation of disease.[4] The roof of the antrum rises posteromedially. Reduction in dose to disease in this region may be produced by the use of an eye shield since the antral roof often rises to the level of the cornea (Fig. 4). There is marked anatomic variation in this respect, however, and evaluation of the individual case is required. Shielding of the eye may also result in decreased dose to the floor of the middle cranial fossa and foramen rotundum. The floor of the anterior cranial fossa and ethmoidal regions may receive insufficient irradiation when the eye is shielded if these areas receive no dose contribution from the lateral field and inadequate dose from a narrow upward prolongation of the anterior field. Shielding of

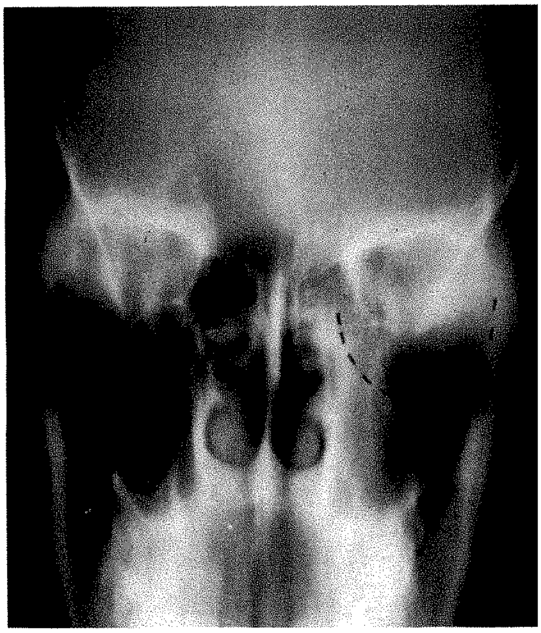

Fig. 4. Tomogram, 5 cm. posteroanterior: The lowe halves of the bony orbits have been outlined b use of the 3 cm. posteroanterior tomogram. Not that approximately one-third of the right maxi lary antrum projects above the inferior orbit rim. Shielding the right eye in such a case coul result in inadequate irradiation of tumor if it o cupied the region of the antral roof, especial medially. There is considerable variability in t degree of upward slope of the posterior antral roc even from one side to the other in the same ind vidual, as shown in this case.

the homolateral eye from irradiation shoul be done only with great care to ensu adequate dosage to all known or probab disease extensions adjacent to the orbit.

RESULTS

An analysis of 5 year survival by site origin (Table II) revealed that the lesior having the most favorable prognosis wer those arising in the nasal cavity (75 pe cent determinate 5 year survival) and the maxillary antrum infrastructure (66 per cent 5 year survival). There were r survivors of the 4 cases classified as havir ethmoidomaxillary tumors. The determ nate 5 year survival for the entire seri was nearly 50 per cent.

The survival rates for the differe methods of treatment (Table III) must

TABLE III

PARANASAL SINUSES—NASAL CAVITY
(1954–1963)
RECURRENCES AND 5 YEAR SURVIVAL BY METHOD OF PRIMARY TREATMENT

Treatment	No. of Patients	Per Cent Recurrences	Per Cent 5 Year Survival	
			Absolute	Determinate
Surgery alone	42	38	61.5	66.7
Irradiation alone	35	26	35.3	40.0
Preoperative irradiation	23	39	31.3	38.5
Postoperative irradiation	15	40	30.0	37.5
Chemotherapy alone	3	—	0	0
Chemotherapy+irradiation	2	—	0	0
No treatment	1	—	0	0
Total Series	121	36	42.5	48.4

interpreted in light of the fact that the choice of treatment was determined by the location and extent of the disease.

The recurrence rate for maxillary sinus infrastructure lesions (Table II) is significantly less than for other sites, largely because of their ready accessibility to surgical extirpation and early onset of symptoms (usually toothache and facial pain). Nasal cavity tumors also recur relatively infrequently. The recurrence rate for the total series was 36 per cent. The difference in recurrence rates among the different methods of primary treatment is not statistically significant. Furthermore, the different groups obviously do not represent comparable groups as the cases were assigned to various treatment methods according to stage and type of disease as mentioned above. It is somewhat surprising that the group treated by irradiation alone did not demonstrate a significantly higher recurrence rate, in view of the fact that many of these patients were treated at an extremely advanced stage of disease.

Of the 121 cases reviewed, the tumor remained localized in 108, of which only 13 had detectable lymph node or distant metastases at any time on follow-up. Forty-four patients with recurrent or persistent disease were studied in an effort to discover, if possible, the cause of the local failure (Table IV). These local failures reflect the difficulty in achieving local control.

In 14 patients, the tumor was so extensive that palliation was the only intent. In the remaining cases, the sites of active disease were most often at the surgical margin or the edge of treatment portals. Shielding of the eye during irradiation or failure to exenterate the orbit in the presence of immediately adjacent tumor resulted in recurrence in 9 cases.

Several illustrative cases are presented to demonstrate the pitfalls in therapy which may result in recurrences.

TABLE IV

ANALYSIS OF 44 LOCAL FAILURES IN 121 PREVIOUSLY UNTREATED MALIGNANT DISEASES OF THE PARANASAL SINUSES AND NASAL CAVITY
(1954–1963)

Radiotherapy*	
Failure of primary lesion to respond	3
Recurrence at margin of treatment field	9
Recurrence in area protected by eye shield	4
Surgery	
Recurrence at margin of resection	11
Known tumor remaining after surgery	3
Massive disease—palliation only	14
Total	44

* Alone or combined with surgery.

ILLUSTRATIVE CASES

Case i. A squamous cell carcinoma of the right antrum with involvement of the right nasal turbinates and orbital floor in a 61 year old white female was treated by radical resection of the right maxilla without orbital exenteration. Twenty months later a recurrence developed in the right inner canthus adjacent to the previous excision. A right orbital exenteration was performed, and the patient is living without evidence of disease 6 years later.

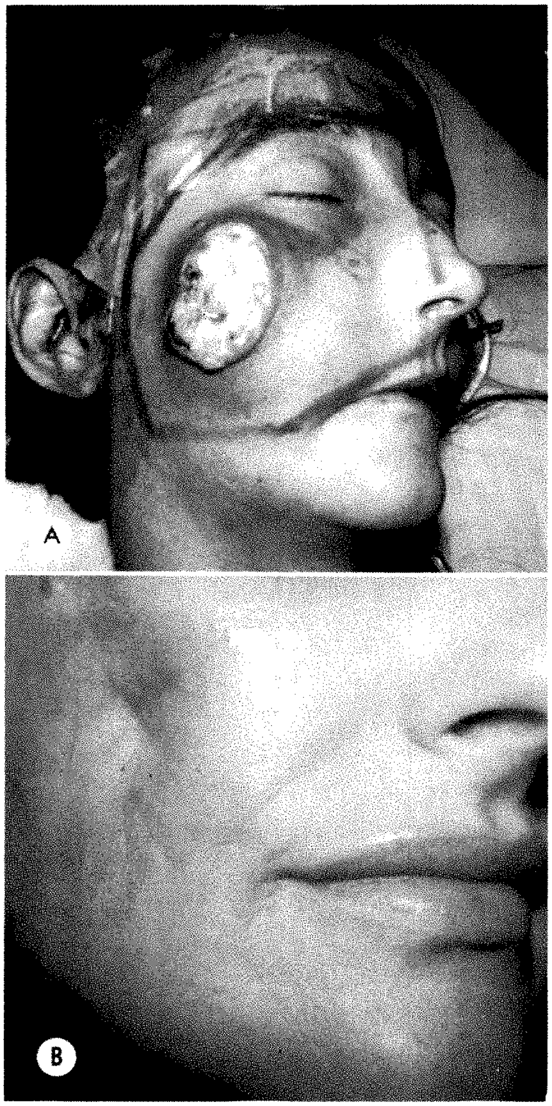

Fig. 5. (*A*) Photograph of the treatment field used for a large cheek recurrence following incomplete radiation therapy for a squamous cell carcinoma of the maxillary sinus infrastructure. Note the catheters for intra-arterial infusion of 5-fluorouracil and methotrexate. During the last half of her course of radiation therapy, the field was reduced to exclude the right eye. (*B*) Appearance of the skin 15 months after treatment of the recurrence.

Case ii. A 59 year old white male with squamous cell carcinoma of the right antrum extending into the nose received preoperatively 5,000 rads tumor dose in 5 weeks from cobalt 60 teletherapy. Anterior and right lateral 45 degree wedge filtered portals were used, with the right eye shielded from both portals. Six weeks later, a right maxillary resection without orbital exenteration was performed. Recurrent tumor developed in the cribriform plate and frontal region 18 months later. This area was not included in the lateral portal in an attempt to preserve vision, and was near the margin of the anterior field, both factors resulting in low dosage.

Case iii. A 27 year old white female with squamous cell carcinoma of the infrastructure of the right maxillary antrum was planned for 5,000 rads tumor dose preoperatively in 5 weeks to be followed by radical surgery with exenteration of the orbit. Anterior and lateral 45 degree wedge filtered portals were used with no eye shield. She did not return for the planned operation because of personal problems, but was seen 2 years later with a massive recurrence anteriorly at the junction of the 2 fields (Fig. 5, *A* and *B*). This area received a low tumor dose but was expected to be removed at operation. For the recurrent disease, she was treated with intra-arterial 5-fluorouracil and methotrexate, plus 5,000 rads given dose to an area which included the right eye during half of the dose. The patient is alive 5 years after her initial treatment, with normal vision and only moderate conjunctival infection in the irradiated eye.

Case iv. A 54 year old white male with adenocarcinoma of the left ethmoid sinuses was treated by maxillary resection with curettement of the ethmoid sinuses and postoperative irradiation using 250 kv. roentgen rays (this patient was treated in 1954). A tumor dose of 6,100 r in 46 days was delivered through cross-firing paired anterior and lateral portals. The lateral portals were angled 20 degrees anteriorly. In spite of a small field at the bregma directed 25 degrees caudad, the dosage in the posterior ethmoid-sphenoid region was low. A

Table V

COMPLICATIONS IN 75 PATIENTS WITH PARANASAL SINUS AND NASAL CAVITY MALIGNANT DISEASES RECEIVING IRRADIATION*
(1954–1963)

Minor		Major	
Exposed bone of maxilla	1	Decreased vision (optic nerve atrophy, retinal or central nervous system damage)	6
Delayed healing postoperatively	4	Central nervous system necrosis (suspected or confirmed)	3
Wound abscess	2	Osteonecrosis (mandible 1, maxilla 1)	2
Epiphora	1		
Cataract	1		
Totals	9 (12%)		11 (15%)

* Total complications-20 (27%).

recurrent mass developed in this area 7 months after completion of therapy.

COMPLICATIONS

The complications encountered in 75 patients receiving irradiation alone or combined with surgical resection are enumerated in Table v. Central nervous system and ocular damage comprised the bulk of major complications. Such risks can be entirely avoided only at the cost of an increase in recurrences due to inadequate irradiation of disease.

SUMMARY

Adequate treatment for carcinomas of the paranasal sinuses and nasal cavity demands a thorough evaluation of the site of origin and routes of spread of the tumor. Roentgenographic examination is the most accurate clinical procedure for obtaining this information.

Detailed roentgenographic examinations are required in order to give the maximal amount of information with respect to the total extent of tumor involvement.

Since these lesions tend to remain localized, the problem is principally one of local control of the disease. Failure to achieve local control has been seen to reflect an initial underestimation of the extent of disease or curtailment in the radicality of the treatment technique in an effort to preserve vision or avoid the risk of complications. In some cases, failure may be due merely to the fact that the disease is so massive that only palliation can be attempted.

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CHANGES IN PULMONARY ARTERIAL PERFUSION DUE TO INTRATHORACIC NEOPLASIA AND IRRADIATION OF THE LUNG*

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THE response of the tissues of the lung to cancericidal levels of ionizing radiation forms a complex pattern of differential damage and repair. The remarkable reserve capacity of the lung in most cases prevents clinical manifestations of radiation-induced injury. Nevertheless, there are few radiotherapists who have not observed an occasional patient in whom severe respiratory insufficiency has followed sterilization of an intrathoracic tumor.

The morphologic changes induced in the lung by irradiation are well-known, having first been described by Groover, Christie and Merritt[5] in 1923, and more recently by Engelstadt[4] and others.[1] However, these changes are significant primarily to the extent that they compromise pulmonary function, often in a lung damaged by preexisting disease. Consequently, investigative interest has focused on measuring parameters of respiratory physiology before, and at intervals after, the administration of ionizing radiation.[3] Teates and Cooper[8] have indicated the difficulties inherent in such studies. These include, but are not limited to, the tendency for compensatory changes in nonirradiated lung to offset radiation-induced impairment of ventilation, perfusion, compliance or alveolocapillary diffusion so that the net detectable change is slight or nil. Thus the patient with roentgenographic evidence of radiation fibrosis may not only be clinically asymptomatic but also have no detectable abnormality of respiratory function.[2] Further, it may be difficult to differentiate changes induced by radiation from those caused by persistence or progression of disease.

Recently, we undertook a prospective study of the effect of (a) intrathoracic neoplasia and (b) ionizing radiation on pulmonary arterial perfusion. This parameter was selected for two reasons: it is a major prerequisite for normal gas exchange in the lung, and it is conveniently studied by pulmonary perfusion scanning, or lung scanning, a safe, simple technique.

The lung scan is an analog display of the distribution in the pulmonary arteriolocapillary bed of approximately 5×10^5 radioactive particles. These particles are composed of clumps or macroaggregates of serum albumin molecules labelled usually with iodine I^{131}. They are passively transported in the blood from the peripheral injection site into the lung. Using a quantitative method of scan analysis, Lopez-Majano and his associates[7] found that the partition of radioactive particles between the two lungs shown by scanning correlated closely with the partition of pulmonary arterial blood measured by differential bronchospirometry. Since particle distribution within the lung is flow-dependent, the number of particles per unit volume of lung, marked by the unit intensity of radioactivity, is proportional to the fractional perfusion of that region. The number of particles lodged in the pulmonary microcirculation remains reasonably constant for a finite period, allowing their photon emission to be mapped by scanning techniques. Although the major clinical use of lung scanning remains the detection of pul-

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monary thromboembolism, the information provided as to the state of pulmonary arterial perfusion is valuable in the investigation of other pulmonary diseases, such as neoplasia and radiation fibrosis.

This report presents our results in 34 patients who underwent intentional or incidental irradiation of the lung. A subsequent report will present quantitative data of pulmonary perfusion changes in animals subjected to graded doses of irradiation to one hemithorax.[6]

MATERIAL AND METHOD

The patients studied included 20 with bronchogenic carcinoma, 7 with carcinoma of the breast, 4 with pulmonary metastases, 2 with intrathoracic lymphoma and 1 with carcinoma of the esophagus. Two patients were studied more than a year after radiation therapy, and 2 others were studied before and after a second course of treatment.

Each patient underwent lung scanning after an intravenous injection of 300 μc of macroaggregated albumin labelled with I^{131}. The specific activity of the radiopharmaceutical was such that the amount of protein administered seldom exceeded 0.5 mg. Thyroidal uptake of I^{131} was blocked by Lugol's solution given for 4 days beginning one day beforehand. A companion chest roentgenogram was obtained at the time of each scan. Follow-up scanning was performed when possible upon completion of radiotherapy and at intervals thereafter.

All scans were begun immediately after injection of the tracer using a rectilinear scanner with a 5 inch scintillation crystal, focussed collimator and pulse height analyzer. Scanning speeds ranged from 120 to 200 cm. per minute.

Scans were evaluated for uniformity of pulmonary arterial perfusion and for the presence, intensity and extent of ischemia. When ischemia was found, the aeration and other roentgenographic features of the ischemic region were noted. Conversely, roentgenographic densities due to tumor, fibrosis or pleural thickening were related to the state of perfusion of the affected area. Follow-up scans were evaluated also for interval changes in perfusion. Densimetric analysis of photoscans was not performed.

RESULTS

ALTERATIONS IN PULMONARY ARTERIAL PERFUSION DUE TO NEOPLASM OF THE LUNG OR MEDIASTINUM

Table I summarizes the findings in 32 patients prior to radiation therapy. Of this group, 25 patients had neoplasms involving the lung or mediastinum. In 5 of these patients pulmonary arterial perfusion was normal. Regional ischemia commensurate with, or less extensive than, the roentgenographic size of the tumor was found in 11 patients (Fig. 1, *A* and *B*). In 9 patients ischemia was disproportionate, being more extensive than would be anticipated from the size of the tumor (Fig. 2, *A* and *B*). All 9 patients had carcinoma of the lung involving the hilus; the tumor was primary in 8 patients and metastatic in 1. However, 3 additional patients with neoplastic involvement of the hilus failed to exhibit dis-

Table I

INITIAL STATUS OF PULMONARY PERFUSION IN 32 PATIENTS PRIOR TO RADIATION THERAPY

Type of Neoplasm		Perfusion: Normal	Ischemia: I≦D	Ischemia: I>D
1° Carcinoma of lung	20	3	9	8
Peripheral	(9)	(3)[a]	(6)	(0)
Hilar	(11)	(0)	(3)	(8)[a]
2° Carcinoma of lung	4	1	2	1[b]
Lymphoma, intrathoracic	1	1	0	0
Carcinoma of esophagus	1	1	0	0
Carcinoma of breast	6	6	0	0
Total	32	12	11	9

I = ischemia, D = roentgenographic density.

[a] 1 patient in this group had previous radiation therapy (total = 2).

[b] Metastasis simulated 1° bronchogenic carcinoma involving hilus.

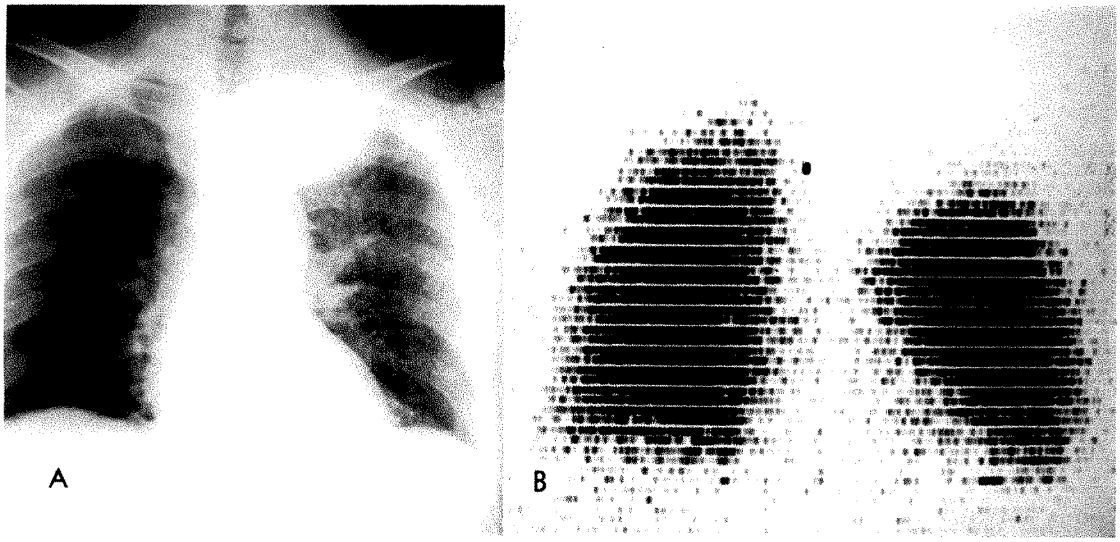

Fig. 1. *Left Superior Sulcus Tumor.* (*A*) The roentgenographic extent of the tumor is commensurate with the ischemia it has produced as shown by the lung scan (*B*). Patient AV, a 47 year old male.

parity between tumor size and extent of ischemia.

ALTERATIONS IN PULMONARY ARTERIAL PERFUSION ATTRIBUTABLE TO IRRADIATION

Table II summarizes the findings in 18 patients whose lungs were irradiated during treatment of neoplasia. In 16 patients studies were performed before treatment and at least once after treatment; 2 of these patients were undergoing treatment for the second time. In 2 other patients who received radiation therapy in the past, only follow-up studies were obtained.

Of the 16 patients studied before and after radiation therapy, there was no de-

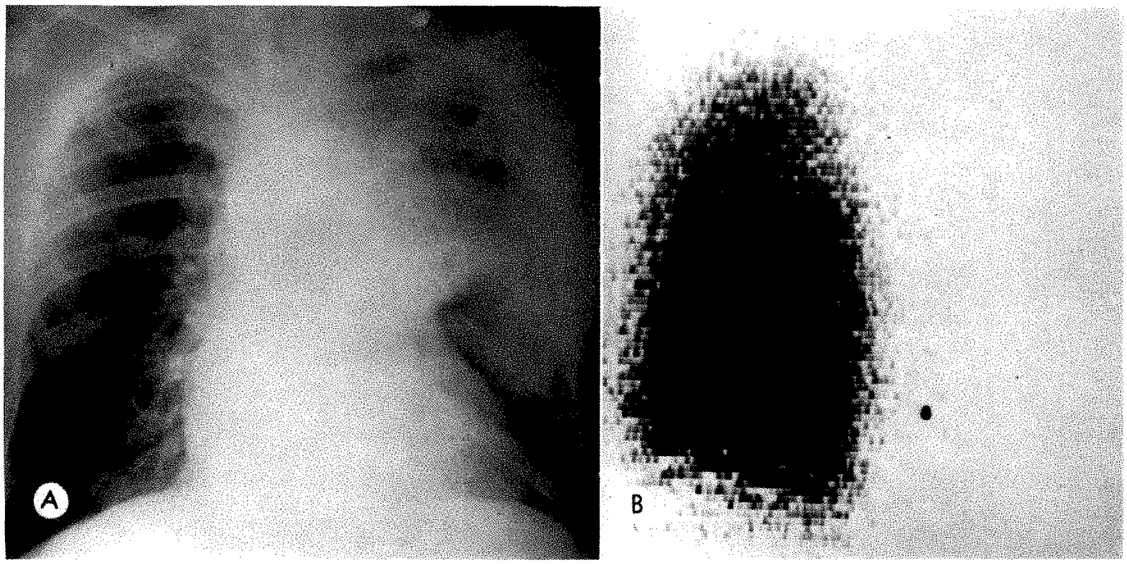

Fig. 2. *Bronchogenic Carcinoma Arising in Left Hilus.* (*A*) Chest roentgenogram discloses a large hilar mass with obstructive features. However, aeration of the lung elsewhere appears normal. (*B*) The lung scan reveals total ischemia of the left lung. See also Figure 5, patient OS.

TABLE II

RESULTS IN 18 PATIENTS AFTER RADIATION THERAPY

Case	Treatment Tumor Dose (rads)	Days	Follow-up at	Change from Initial Scan and Roentgenogram
A. 1° Carcinoma of Lung				
OS	3,000	14	3 mo.	Restored perfusion; tumo shrinkage
BP	4,000	19	8 mo.	No change; normal; 2,500 r in 1 days given 15 months earlie
WP	4,400	35	3 mo.	Increased ischemia; fibrosis
AI	4,500	30	7, 12 mo.	Increased ischemia and fibrosis treated in past (dose un known)
RC	4,900	26	1, 7, 22 mo.	Increased ischemia; fibrosis
MM	5,000	35	2, 5 mo.	None; total ischemia
AW	5,000	43	0, 8 mo.	Ischemia and fibrosis at months; emphysema un changed
1*	2,400	17	11 mo.	
NS	1,200	6	1.5 mo.	No change; normal
B. 2° Carcinoma of Lung				
WS	1,500	12	0 mo.	No change; irregular perfusio bilaterally
C. Carcinoma of Esophagus				
MS	5,400	38	1 mo.	No change; slight ischemia o lower left lung
D. Carcinoma of Breast				
LH	3,200	25	11 mo.	No change; normal
GH	4,100	36	1 mo.	No change except ? silen embolus
SM	4,400	31	0, 9, 22 mo.	Transient ischemia and cloudin of apex
RR	4,500	30	1.5 mo.	No change; normal
RK	4,500	32	6 mo.	Ischemia of apex, marked; sligh fibrosis
JH	5,200	34	1, 5 mo.	Progressive ischemia and pleura thickening of apex
E. Post-Treatment Study Only				
LB	Unknown		14 yr.	Ischemia and fibrosis (carcinom of breast)
SB	2,200 r	20	8 yr.	Ischemia and fibrosis (Hodg kin's disease)
	4,200 r	45	1 yr.	

* 1 = reticulum cell sarcoma of lung and thorax.

tectable interval change in pulmonary arterial perfusion in 8. Seven of these patients were treated with intent to cure. A *de novo* appearance of ischemia (Fig. 3, *A–D*; and 4, *A–D*) or increase in pre-existing ischemia was observed in 7 patients. In 1 patient pulmonary perfusion showed significant net improvement following treatment (Fig. 5, *A* and *B*). Evidence o ischemia was found in the 2 patient treated previously (Fig. 6, *A* and *B*).

Roentgenographic changes compatibl with "radiation pneumonitis," radiatio fibrosis or pleural thickening were observe in all 9 patients manifesting newly de veloped or increased ischemia. These in

cluded 4 patients with primary carcinoma of the lung, 1 with intrathoracic lymphoma and 4 with carcinoma of the breast. All had received treatment with supervoltage radiation given with intent to cure. However, the postirradiation changes in the lung or pleura did not exceed, and usually were less marked than, the degree of ischemia (Fig. 3, *A–D*).

DISCUSSION

The results of this study indicate that peripheral lung tumors produce pulmonary arterial perfusion deficits commensurate with their size. Due to the limited resolution of present scanning equipment, perfusion deficits caused by lesions under 2 cm. in diameter are usually undetectable. However, when a lung tumor is located in the hilus there is a great probability of extensive impairment of perfusion of the ipsilateral lung, as observed in 9 of 12 patients in this series.

There are two mechanisms by which a hilar neoplasm may reduce pulmonary arterial flow. The first is the effect of the physical bulk of the tumor on the pulmonary artery, which may narrow the vessel by compression or direct invasion. That reduction of tumor bulk may lead to improved perfusion is shown by the response in patient OS (Fig. 2, *A* and *B*; and 5, *A* and *B*), in whom partial restoration of perfusion of a totally ischemic lung followed shrinkage of the tumor by irradiation. Wagner and his associates[9] found that inflation of a balloon catheter within a segmental bronchus, with preservation of "adequate" air flow, caused ischemia of the canine lung. As a result they have questioned whether carcinoma arising in a bronchus may not impair flow through the accompanying pulmonary artery.

The second mechanism is the shunting of arterial blood at systemic pressure into the pulmonary artery via neovascular collateral channels arising in the tumor, which is supplied by the bronchial arteries. However, in the absence of quantitative supporting data, it seems unlikely that such

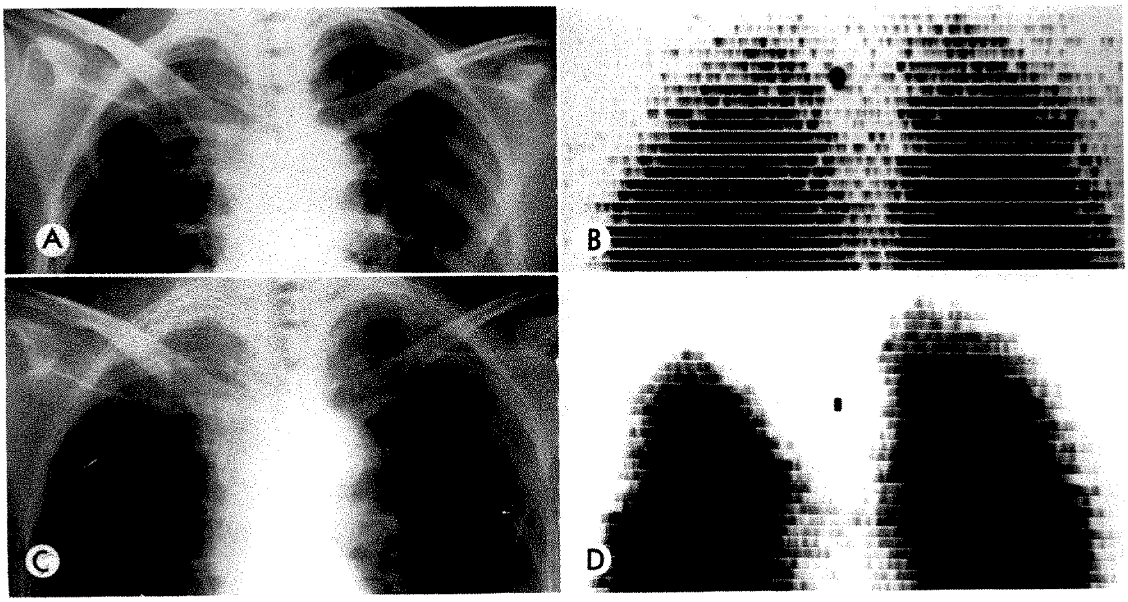

Fig. 3. *Carcinoma of Breast.* (*A*) Preirradiation chest roentgenogram and (*B*) lung scan show slight apical pleural thickening and irregular perfusion of the apices respectively. The latter is a common finding. A tumor dose of 4,500 r in 4.5 weeks was then given to the right breast, supraclavicular and internal mammary regions with supervoltage equipment. (*C*) Six months after completion of treatment, the right apex shows increased pleural thickening and (*D*) there is markedly impaired perfusion by lung scanning. Patient RK, a 50 year old female.

shunts are hemodynamically significant.

It would appear desirable to determine if there is a relationship between altered pulmonary perfusion and surgical resectability of neoplasms that involve the hilus.

The utility of the lung scan in detecting postirradiation perfusion changes is evident in our results. There were 9 of 18 patients in whom ischemia occurred in the irradiated region of the lung—an incidence somewhat lower than that reported by Bate and Guttmann.[2] This may reflect the shorter

FIG. 4. *Carcinoma of Lung, Peripheral.* (*A*) Initial roentgenogram and (*B*) lung scan prior to treatment and 1 month after resection of a 1 cm. bronchogenic carcinoma from the right mid-lung. Despite emphysema, pulmonary perfusion is normal except in the upper third of the left lung. (*C*) Follow-up roentgenogram and (*D*) scan were obtained 8 months after delivery of 5,000 r tumor dose to the tumor bed in 43 days using supervoltage equipment. Fibrosis and ischemia in the irradiated region are discrete, localized and commensurate. Patient AW, a 69 year old male.

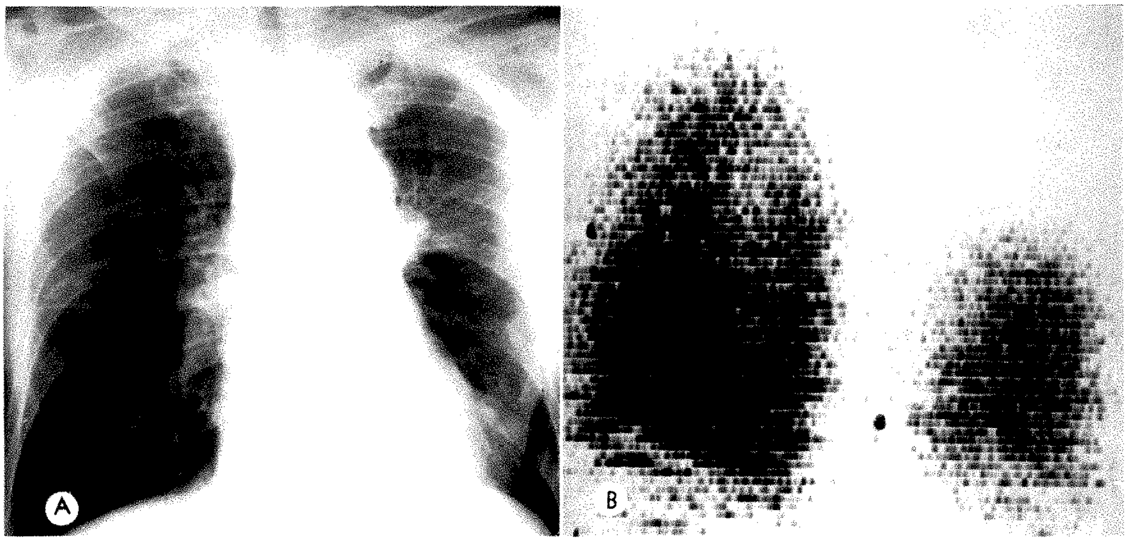

Fig. 5. *Net Improvement of Perfusion Following Radiotherapy.* (*A*) Follow-up roentgenogram and (*B*) scan in patient OS 3 months after delivery of 3,000 r tumor dose in 14 days using supervoltage equipment. Comparison with initial examination (Fig. 2, *A* and *B*) shows marked reduction in tumor volume and return of perfusion to the lower half of the left lung. However, the appearance of ischemia in the upper half of the right lung suggests compromise of the right pulmonary artery by tumor extending across the mediastinum. The patient died shortly thereafter.

mean period of follow-up in our series. Associated roentgenographic evidence of pleural or pulmonary reaction to radiation was present in these 9 patients but in general was less marked than the alteration of perfusion. Since the extent of regional ischemia cannot necessarily be inferred from the chest roentgenogram, it would appear reasonable to employ the lung scan more widely in patients undergoing irradiation of the chest, particularly those who present clinical symptoms of "radiation pneumonitis" or respiratory insufficiency after treatment. No other method of

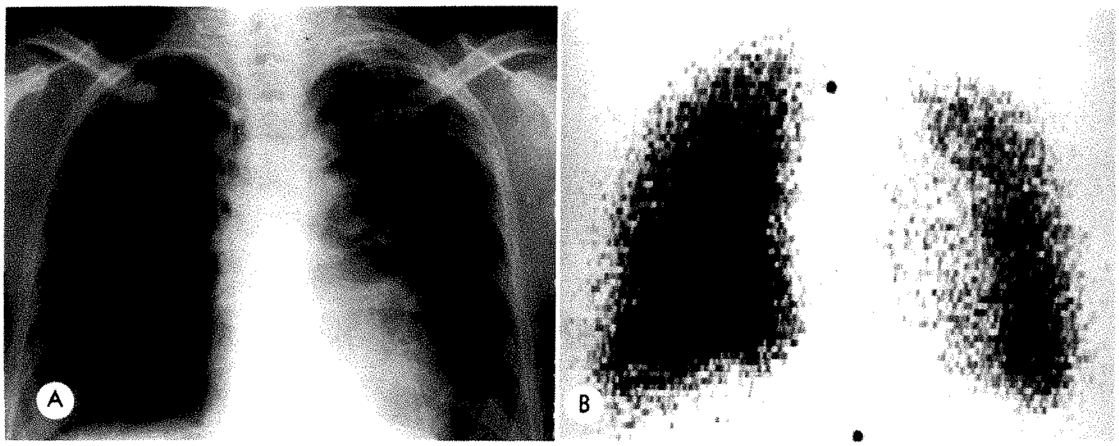

Fig. 6. *Ischemia and Radiation Fibrosis Following Remote Irradiation.* Patient SB, a 31 year old female, had received tumor doses of 2,200 r in 20 days and 4,200 r in 45 days, 8 and 1 years before examination respectively. She had Hodgkin's granuloma involving the mediastinum. (*A*) Roentgenogram reveals paramediastinal fibrosis, chiefly left-sided. (*B*) Lung scan discloses moderately impaired perfusion of the entire left lung except in the lower third.

comparable ease or simplicity exists for detecting regional changes in pulmonary blood flow.

SUMMARY AND CONCLUSIONS

1. Pulmonary arterial perfusion was evaluated by lung scanning in 34 patients with neoplasms of the chest or breast.

2. In 9 of 12 patients with neoplasms involving the hilus of the lung, disproportionate ischemia of that lung was present prior to treatment, whereas with peripheral tumors ischemia was commensurate with the size of the lesion.

3. Pulmonary ischemia attributable to irradiation was demonstrable in 7 of 16 patients examined after treatment. Ischemia was also found in 2 additional patients treated in the past. Roentgenographic changes of radiation-induced injury to lung or pleura were observed in these 9 patients but in general were less marked than alterations in perfusion.

4. The information uniquely provided by lung scanning commends greater use of this simple procedure in patients receiving radiotherapy for lesions of the lung, breast and mediastinum.

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The authors gratefully acknowledge the assistance of Bruce R. Parker, M.D., Pearl S. Varian, Cecilia McRae and Barbara Cravitz.

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curves, Quimby's experiment on the threshold erythema dose led to the most useful iso-effect curve. Strandqvist's curve, for skin cancer and second degree erythema, although based on a single lesion in each patient and therefore lacking in corroboration, has clinical validity because of the care in its derivation and construction.

The ideal test object (Fig. 6) consists of multiple similar tumors in the same patient. In this way we have studied recurrent chest wall nodules of breast cancer,[5] mycosis fungoides,[6] and Hodgkin's disease.[7]

As the succession of new but similar lesions in Case I emerged, we became aware of the unique opportunity to conduct a time-dose study leading to the construction of an iso-effect recovery curve for this exceedingly rare lesion. In this particular patient, the choice of tumor doses, some of which were obviously excessive and others inadequate, was dictated by our interest in defining the parameters of the recovery curve.

The data from Case I are assembled in a scatter diagram in Figure 4. The solid dots represent successful doses which destroyed the tumor for 3 to 18 years. Doses that failed to destroy the tumor are shown as open circles. The data did not lend themselves to mathematical analysis; therefore, a freehand iso-effect recovery curve was drawn to delineate an optimum time-dose zone just above the sublethal range. All doses below the curve, with one exception, failed to destroy the tumor. While this recovery curve is valid for this patient only, it is clinically useful. On the basis of this curve, one may reasonably state that a useful tumor lethal dose for giant cell tumor of bone arising in Paget's disease should be in the range of 2,500 to 3,000 rads in 15 days. The "equivalent single dose" is 1,900 rads.

TABLE II

CALCULATED RECOVERY FACTOR FOR VARIOUS TISSUES

Author	Tissue	Recovery Factor
Cohen[2]	Breast cancer	0.34
Cohen[3]	Skin (erythema)	0.33
Quimby and MacComb[13]	Skin (erythema)	0.22
Strandqvist[19]	Skin cancer	0.31
Friedman and Pearlman[5]	Recurrent breast cancer	0.25
Friedman and Pearlman[6]	Mycosis fungoides Mycosis fungoides	0.12 0.40
Friedman *et al.*[7]	Hodgkin's disease	0.25
Scott and Brizel[17]	Hodgkin's disease orthovoltage supervoltage	 0.33 0.29
Pearlman and Friedman (Present series)	Giant cell tumor on Paget's disease of bone	0.09

THE CALCULATED RECOVERY FACTOR

The calculated recovery factor for various tumors and for normal skin has been derived by several authors (Table II). It defines the slope of the iso-effect recovery curve on a log-log graph. Slopes higher than 0.20 indicate significant recovery. The recovery factor for Case I (benign giant cell tumor) is 0.09. This is the lowest recovery factor in our experience (Fig. 5). It suggests that fractionation plays a less significant role in the treatment of this type of giant cell tumor than for the other tumors listed in Table II. It may also explain the successful technique of earlier years, whereby giant cell tumors were treated with several courses of irradiation of relatively small doses in the range of approximately 2,000 r per course.

EQUIVALENT SINGLE DOSE (ESD)

The lethal dose of a particular tumor may be symbolized by an equivalent dose given in a single exposure. The ESD may be obtained by either of two methods: irra-

TABLE III

EQUIVALENT SINGLE DOSES (ESD)

Lesion	Equivalent Single Dose	Author	Method of Derivation
Recurrent breast cancer	2,000 r	Friedman and Pearlman[5]	MCTLD*
Mycosis fungoides Case I	800 r	Friedman and Pearlman[6]	MCTLD
Mycosis fungoides Case II	250 r	Friedman and Pearlman[6]	MCTLD
Skin cancer	2,200 r	Strandqvist[19]	Statistical average
Skin cancer	2,050 r	Ellis[4]	Statistics
Hodgkin's disease	1,178 rads	Friedman *et al.*[7]	MCTLD
Hodgkin's disease	1,750 rads	Friedman *et al.*[7]	Clinical approximation
Giant cell tumor of bone on Paget's disease (Present series)	1,900 r	Pearlman and Friedman	MCTLD

* MCTLD = minimum corroborated tumor lethal dose.

diating with single doses of different magnitudes until the smallest effective dose is established (minimum corroborated tumor lethal dose), or by extrapolating the iso-effect tumor lethal dose curve back to the ordinate representing a single exposure. In this study of giant cell tumors, the equivalent single dose was 1,900 rads and was established by the former method. A number of equivalent single doses for various diseases are tabulated in Table III. The ESD is a useful radiobiologic symbol of radiosensitivity, although its clinical significance remains to be established.

The cluster of tumors having an equivalent single dose in the 2,000 rad level (Table III) calls to mind radiobiologic studies of tissue cultures of many different tumors. It is of interest, and it may be significant, that the tumor lethal dose of these tumors tends to be similar.

CONCLUSIONS

1. Giant cell tumor arising in Paget's disease of bone is rare and usually follows a benign course. The few cases reported in the literature were cured by surgery. We believe that irradiation can cure some of these lesions.

2. A clinically useful dose range for this tumor is 2,500 to 3,000 rads in 15 days.

3. An iso-effect recovery curve based on 27 time-dose points in 1 patient was constructed using the "minimum corroborated tumor lethal dose" tactic. The calculated recovery factor of 0.09 suggests minimal tumor recovery between dose fractions for benign giant cell tumor of bone.

4. The equivalent single dose (ESD) for giant cell tumor of bone is 1,900 rads.

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CLINICAL CONSIDERATIONS AND TREATMENT OF *IN SITU* LOBULAR BREAST CANCER*

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In situ lobular cancer belongs to a relatively small group of noninfiltrating mammary carcinomas that are considered histologically malignant but without demonstrable invasion of the surrounding tissues. While there may be doubt on the part of some pathologists and clinicians that all of these lesions are true cancers, there is accumulating evidence of their infiltrative potentialities. The reports of Antonius and Jones,[1] Benfield, Jacobson and Warner,[2] Godwin,[4] and Newman[7] indicate the risk of infiltrating cancer subsequently appearing in breasts where limited surgery was performed. A recent and excellent study by McDivitt, Hutter, Foote and Stewart[5] covers a long-term follow-up on patients who had *in situ* lobular carcinoma during the years 1941–1952. Among those who were treated by local excisions only, the cumulative risk of developing infiltrative carcinoma was 10 per cent at the end of 5 years, 15 per cent after 10 years, 30 per cent after 15 years and about 35 per cent after 20 years. Also, they emphasized the high risk of carcinoma developing in the contralateral breast during this time.

INCIDENCE

At the Memorial Hospital, from 1949 through 1965, 403 patients were classified as having noninfiltrating cancers of the breast (Fig. 1). Of this group, only 1 patient in 1949 was found to have *in situ* lobular cancer, whereas by 1965 this diagnosis was made in 35 (70 per cent) of the 50 cases of noninfiltrating cancer. We have attributed this increasing recognition to several factors: first, the careful microscopic examination of more randomized sections of tissue from benign gross specimens; second, wider and more frequent diagnostic local excisions; and, lastly, mammograms have been helpful in a few selected cases. Mammograms of operative specimens, as suggested by Snyder,[8] have in some instances enabled our pathologist to select areas for microscopic studies that otherwise would have been overlooked.

Of the 403 patients diagnosed as having noninfiltrating cancer, 161 (40 per cent) were classified as having *in situ* lobular carcinoma (Table 1). An additional 36 patients had a combination of this lesion and *in situ* cancer which apparently arose in the terminal ducts of the lobules. This is a total of 197 (48.8 per cent) with *in situ* lobular cancers out of the entire series of noninfiltrating cancers. Twenty (10 per cent) of these 197 patients had simul-

Fig. 1. Incidence of noninfiltrating breast cancer treated at Memorial Hospital from 1949 through 1965 in 403 patients.

* Presented at the Forty-ninth Annual Meeting of the American Radium Society, Toronto, Ontario, Canada, May 29–31, 1967. From the Memorial Hospital, New York, New York.

TABLE I

403 PATIENTS WITH NONINFILTRATING BREAST CANCERS MEMORIAL HOSPITAL 1949–1965

Pathologic Diagnosis	Total Patients: Unilateral Tumors	Per cent of Unilateral Tumors	Bilateral Simultaneous Tumors
In situ lobular carcinoma	144	38	17 (10.6%)
Noninfiltrating duct carcinoma and *in situ* lobular carcinoma	33	9	3 (8.3%)
Intraductal carcinoma	128	33	1 (0.8%)
Paget's disease of nipple	44	11	—
Papillary noninfiltrating carcinoma	15	4	—
Intracystic carcinoma	4	1	—
Other noninfiltrating carcinoma	14	4	—
Totals	382	100	21

taneous bilateral *in situ* lesions, whereas bilaterality was extremely uncommon in other types of noninfiltrating cancers.

AGE DISTRIBUTION, MENSTRUAL AND MARITAL STATUS

The ages varied from 26 to 70 years, the median being 47 years (Fig. 2). One hundred and three patients were having regular menses and the periods of 29 were listed as irregular. Therefore, 132 (66.6 per cent) were showing active or declining ovarian function. This percentage is almost double that found in patients having infiltrating breast cancers. It would appear that *in situ* lobular cancer is less likely to occur in postmenopausal and involuting breasts where the lobular and terminal duct cell population is limited.

Only 21 of the series of 197 patients were never married. Of those married, the majority had 1 to 3 children but only 34 gave a history of having nursed them.

SYMPTOMS AND PHYSICAL FINDINGS

Seventy patients had no symptoms. Fifty-five had experienced mild pain and 109 had what they described as a "lump." A bloody nipple discharge had been noted by 12 patients and 5 others gave a history of a serous nipple discharge.

The physical findings were minimal or absent for diagnosis of cancer. Fifty-seven patients were described as having a poorly defined thickening, 143 a discrete mass and in 18 a nipple discharge was noted. In most instances the "discrete mass" could best be described as an area of increased density with varying degrees of marginal definition. Only 13 patients were considered to have skin adherence and in none of these was there actual dimpling. With very few exceptions, the patients were clinically diagnosed as having benign lesions (Table II).

HISTOLOGIC DIAGNOSIS

Similar diagnostic difficulties were experienced with frozen sections (Table III). Of the 190 specimens submitted for frozen sections, 129 (69 per cent) were reported as benign, 34 suspicious (hold for quick

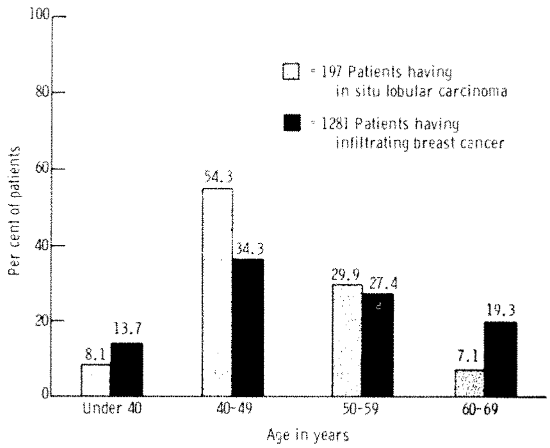

FIG. 2. Age distribution of patients with *in situ* lobular carcinoma and those with infiltrating breast cancer.

Table II

CLINICAL DIAGNOSIS

	In situ Lobular	*In situ* Lobular and Non-infiltrating Duct
Infiltrating duct carcinoma	15	9
Noninfiltrating carcinoma	1	3
Fibrous mastopathy	53	6
Cystic disease	68	10
Intraductal papilloma	9	6
Other	43	9

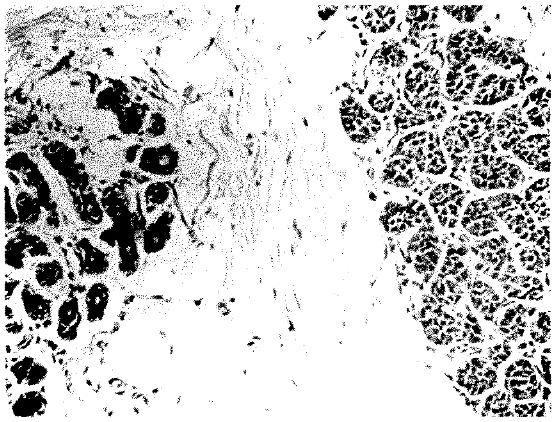

Fig. 3. Photomicrograph showing a normal breast lobule on the left and *in situ* carcinoma on the right.

fixed section) and 27 were diagnosed as noninfiltrating cancer.

When *in situ* lobular cancer appears, the epithelial cells microscopically are no longer cuboidal in shape with the usual acinus arrangement. The cells become loose, larger and rounded with a loss of polarity. The lobule becomes distended with disorganized pale-staining anaplastic cells (Fig. 3 and 4). There is a disappearance of the supporting stroma; mitosis is relatively uncommon. Multiple foci are frequently found in many areas of the breast. The time required for a breakthrough with infiltration of the surrounding tissues (Fig. 5) is not known.

For many years previously these changes

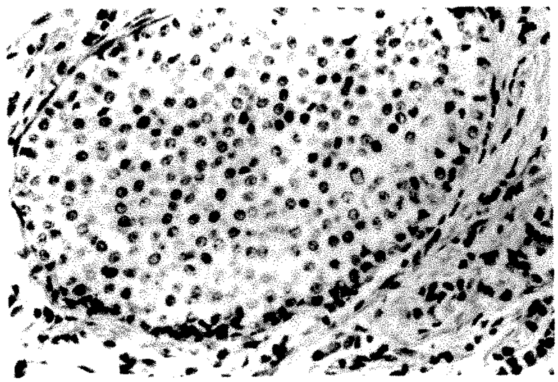

Fig. 4. An acinus distended with *in situ* lobular carcinoma cells and early infiltrating cancer at the lower right margin.

Table III

HISTOLOGIC DIAGNOSIS

Frozen Section Diagnosis	*In situ* Lobular Carcinoma		*In situ* Lobular and Non-infiltrating Duct Carcinoma		Total Tumors
	Unilateral Tumors	Bilateral Tumors	Unilateral Tumors	Bilateral Tumors	
Benign	88	25	14	2	129
Suspicious (hold for fixed section)	19	7	7	1	34
Malignant	13	2	9	3	27
Not Applicable	24	—	3	—	27
Total	144	34	33	6	217

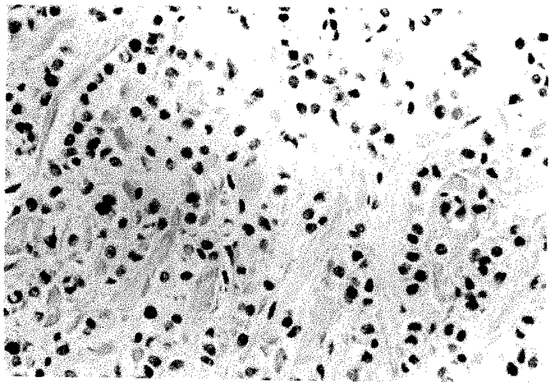

FIG. 5. Infiltrating lobular carcinoma.

were observed but they were not considered cancerous until 1941 when, independently and almost simultaneously, Muir[6] reported such lesions as (*in situ*) intra-acinus carcinoma while Foote and Stewart[3] reported them as lobular carcinoma *in situ*.

TREATMENT

Treatment has varied from generous local excisions to radical mastectomies (Table IV). Today, with few exceptions, we favor and do a modified radical mastectomy, *i.e.*, a simple mastectomy with a partial axillary dissection without removal of the pectoral muscles. Our major reason for this operation is that 79 (67 per cent) of 118 mastectomy specimens revealed residual *in situ* lobular or noninfiltrating cancer following local excisions. The purpose of the partial axillary dissection is the possibility that, despite a most careful gross and microscopic examination, a minute area of infiltration may have escaped detection. In this series of *in situ* lobular carcinomas, none of the specimens has shown axillary lymph node metastases.

TABLE IV

TREATMENT

	In situ Lobular Carcinoma (patients)	*In situ* Lobular and Noninfiltrating Duct Carcinoma (patients)	Totals
Local excision	29	3	32
Simple mastectomy	23	6	29
Modified mastectomy	91	14	105
Radical mastectomy	21	13	34
Total	161	36	197

TABLE V

PATIENTS HAVING *IN SITU* LOBULAR OR NONINFILTRATING DUCT AND *IN SITU* CARCINOMA WITH PATHOLOGY IN OPPOSITE BREAST

Time Period in Relation to Diagnosis of Noninfiltrating Cancer	Benign	Noninfiltrating Cancer	Infiltrating Cancer
Previous	68	—	21
Simultaneous	—	20	17
Subsequent	19	11	3
Total Patients	87	31	41

BILATERALITY

The frequency of simultaneous bilateral *in situ* lobular carcinoma was 10 per cent in this series of 197 cases. Of further interest is the pathology found in the opposite breast, not only simultaneously but before and after the treatment for *in situ* lobular cancer. It is particularly noteworthy that 41 (20.7 per cent) of these patients had infiltrating cancers while 11 others subsequently had noninfiltrating carcinoma (Table V). These observations have prompted us to perform an increasing number of excisional biopsies of the opposite breast, even though the physical and mammographic findings are minimal.

SUMMARY

In situ lobular carcinoma of the breast is relatively uncommon but represents the earliest of the early cancers which occur in the mammary gland. Because of obscure

physical findings, it is rarely diagnosed clinically and frequently missed in gross and quick frozen section examinations. A considerable majority of the breasts show a multicentric origin of *in situ* lobular cancer and there is a high risk of leaving residual disease after a generous local excision.

The frequency and the time at which a breakthrough will occur with resulting infiltration are not known but it seems to be a matter of years rather than months. Only one of the 31 patients listed as having been treated by local excisions in this series is known to have subsequently developed infiltrating cancer in the same breast. Most of these cases, however, were reported as showing only a single or very few microscopic foci of *in situ* lobular cancer in the multiple fixed sections from a local excision. Quite clearly we need to know more about the natural course of this disease but, unfortunately, unlike the cervix, the breast is not easily subjected to frequent cytologic examinations.

The high incidence of *in situ* cancer and/or infiltrating cancer in the opposite breast has been stressed.

Finally, I would like to emphasize that those of us on the Breast Service at the Memorial Hospital believe that the long-term infiltrative potentialities of *in situ* lobular cancer should not be underestimated and that in most patients the best treatment is a modified radical mastectomy. All of the patients so treated have shown no clinical evidence of recurrent disease.

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PRELIMINARY EXPERIENCE WITH PERMANENT INTERSTITIAL IMPLANTS USING CHROMIUM 51 SOURCES*

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At the 1958 meeting of the American Radium Society, Myers[4,5] described the possible application of radioactive chromium 51 gamma ray sources for interstitial radiation therapy and compared the properties of these sources with the physical properties of a number of other isotopes. Recently, Henschke, Lawrence and co-workers[1,3] have reviewed the experience using permanent interstitial implants of several long-lived isotopes. Chromium 51 has a physical half-life of 27 days and a decay scheme as shown in Figure 1. It decays to vanadium 51 with the emission of a 323 kev. gamma ray in approximately 10 per cent of the time, and with the emission of soft x rays of less than 10 kilovolts. These soft x rays are almost completely absorbed by the chromium source itself. The decay scheme shows that no beta particles are emitted, making this isotope a desirable one for interstitial implantation. The I_γ is 0.18 r per hour at 1 cm. from a 1 mc source.[6] Myers[5] described the fabrication of several sources of different sizes. Our method of fabricating sources is slightly different and was suggested by Mr. Gene Asai of the United States Bureau of Mines.

MATERIAL AND METHOD

Highly pure chromium wire is drawn to proper diameter by passing the wire through a heated die which is brought to a temperature of 350°C. At this temperature, chromium may be drawn to proper sizes quite easily and may also be sheared and cut very accurately to proper length. The highly pure, nonradioactive chromium wire was drawn to the diameter of 0.031 inches by the United States Bureau of Mines. In our laboratory we use a special jig and shearing device in a heated oven to shear cylinders 2.5 mm. long from this wire. These sources are then loaded into aluminum cartridges supplied with the implantation gun, which is a modification of the gun described by Hodt, Sinclair and Smithers.[2] This gun is commercially available and is shown in Figure 2. Also shown is the stainless steel sterilization container. Activation of these sources was carried out by the Argonne National Laboratory in the research reactor CP-5.

The source strength that proved most useful was between 4 and 6 mc per seed. Activation took 2 or 3 days. Following activation, these seeds were calibrated by means of Lauritsen quartz-fiber electroscope and compared with a radium standard. A second source was dissolved in strong acid and an alliquot of chromium solution was counted for activity and compared with a liquid standard. The

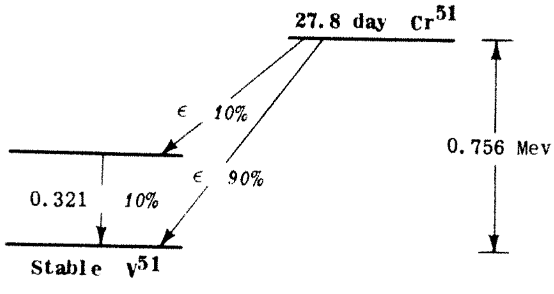

Fig. 1. Decay scheme of radioactive chromium 51.[6]

* Presented at the Forty-ninth Annual Meeting of the American Radium Society, Toronto, Ontario, Canada, May 29–31, 1967.
From the Department of Radiology, Department of Surgery and the Argonne Cancer Research Hospital operated by The University of Chicago for the United States Atomic Energy Commission, The University of Chicago, Chicago, Illinois.
† Career Research Development Award Number 5K3CA 19415.

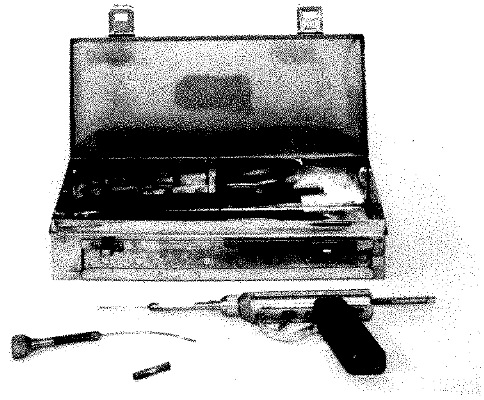

Fig. 2. Implantation gun showing aluminum cartridge, straight and curved needles and stainless steel sterilizing container.

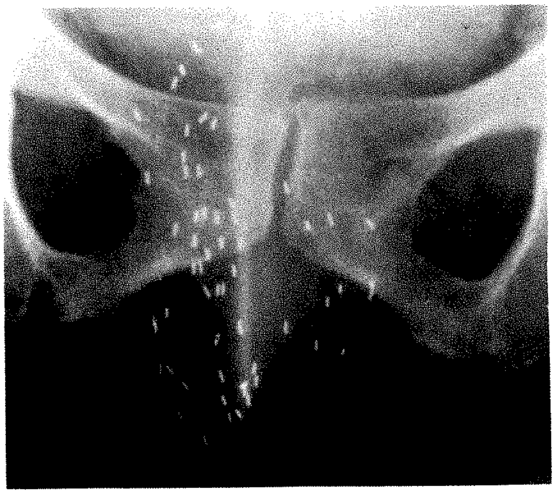

Fig. 3. Roentgenogram showing the placement of the seeds.

two methods of calibration of the sources compared favorably, there being differences of less than 10 per cent between them.

Our first permanent chromium implant was made in a patient with metastases to the presacral area following an abdominal perineal resection for squamous cell carcinoma of the anus. The carcinoma was 6 cm. in diameter and the chromium sources were implanted percutaneously through the perineum. Long spinal 18 gauge needles were positioned throughout the tumor and their positions were roentgenographed. Following adjustment of the position of the needles, the lesion was implanted sequentially by removing the spinal needles and implanting the needle track with chromium seeds using the implantation gun. One chromium

Table I

FAVORABLE RESPONSE

Patient	Diagnosis	Previous Treatment	No. of Chromium Seeds and Activity	Calculated Dose	Comments
Q.D.	Carcinoma of anus	Surgery	60–3.55 mc	5,500 rads	7.5 years without recurrence
C.S.	Carcinoma of cervix, recurrent	Roentgen therapy and radium	57–2.00 mc	3,000 rads	Abdominal implant. Fistula in bladder 2 years after implant
E.D.	Carcinoma of breast	Roentgen therapy	19–3.00 mc	4,600 rads	Recurrence at edge of implant 1.5 years
M.V.	Squamous cell carcinoma of base of tongue	Roentgen therapy	5–3.15 mc	3,000 rads	Implant in metastatic lymph node. Excellent response. No tumor in lymph node at autopsy
A.N.	Carcinoma of pyriform sinus	Surgery and roentgen therapy	9–3.55 mc 3–2.88 mc	6,000 rads	Treatment of recurrence about tracheotomy stoma. No slough
R.K.	Squamous cell carcinoma of palate, anterior pillar, posterior tongue	Roentgen therapy	17–4.50 mc	6,000 rads	Excellent local result, recurrence adjacent to implant
W.Z.	Neck metastases, squamous cell carcinoma	Roentgen and electron therapy	22–4.00 mc 14–5.00 mc 21–4.50 mc	6,000 to 6,500 rads	All lesions responded dramatically to implants
A.K.	Squamous cell carcinoma of cervix with vaginal recurrence	Roentgen therapy, radium applicators and radium implants	12–4.00 mc 14–4.60 mc	5,000 to 5,600 rads	1 cm. ulcer. 8 months after implant. Good local control
M.S.	Squamous cell carcinoma of tongue	Roentgen therapy	3–2.70 mc	6,000 rads	No recurrence at 6 months

Table II

GOOD RESPONSE

Patient	Diagnosis	Previous Treatment	No. of Chromium Seeds and Activity	Calculated Dose	Comments
J.F.	Squamous cell carcinoma of posterior tongue	Roentgen therapy	14–4.10 mc	6,000 rads	Good response in the tongue for 6 months. Lymph node metastases
O.O.	Squamous cell carcinoma of larynx	Roentgen therapy and surgery	41–3.50 mc	5,500 rads	Excellent response in neck metastases for 4 months
G.P.	Carcinoma of oral pharynx	Roentgen therapy	13–4.80 mc	6,800 rads	Autopsy revealed fibrosis and necrosis in the region of the implant. Patient died of distant metastases
E.C.	Carcinoma of cervix with pelvic metastases	Roentgen therapy and radium	22–3.90 mc	5,000 rads	Good response of pelvic mass 4 months after implant
R.C.	Carcinoma of breast with skin metastases	Surgery and roentgen therapy	13–4.50 mc	6,500 rads	New lesions adjacent to implant 4 months following. Treated area shows no recurrence
D.K.	Carcinoma of larynx	Roentgen therapy and surgery	14–2.88 mc	4,000 rads	Marked decrease in size of neck metastases
L.M.	Squamous cell carcinoma of penis with lymph node metastases	Roentgen therapy	15–4.20 mc 52–4.60 mc	5,500 to 6,000 rads	Marked shrinkage of lymph node metastases. Penile lesion showed small 1 cm. ulceration
C.D.	Squamous cell carcinoma of anus	Surgery	19–4.50 mc	5,500 rads	No palpable recurrence 5 months after implant
J.A.	Adenocarcinoma of rectum	Surgery and roentgen therapy	27–3.50 mc	3,400 rads	Good pain relief and decrease of the tumor size for 3 months

source or seed was placed in each cubic centimeter of the tumor (Fig. 3). Sixty seeds, each 3.55 mc, were implanted in the tumor giving an estimated tumor dose of 5,500 rads. Because certain authorities at that time expressed concern over the possible radiation hazard, no further implants were carried out for several years. Although the patient had initially 213 mc of chromium in a permanent implant, only 10 per cent of the isotope decays with a sufficiently energetic gamma ray to be detected. The chromium is extremely inert and no radioactivity was found in either the stool, urine, or expired air.

This patient has remained asymptomatic. Pelvic examination shows an indurated area in the region of the previously described mass, but there has been no progression in this area, nor have metastases been observed in over 7½ years.

Two years ago we received permission to continue clinical investigation of these sources provided the patients with such implants were correctly identified by an arm band and a wallet card. Since that time 24 patients have received 30 implants. Most of these patients have received maximum therapy from external beam radiation and from radium. Some of the patients have had radical surgery and chemotherapy, including perfusion. Tables I, II and III outline the experience in these patients. We have seen necrosis and hemorrhage in 3 instances. This has occurred in patients who have been heavily irradiated previous to implantation of the chromium. Four patients have had 2 implants and 1 patient has had 3 implants. Where we have made repeated implants we have used seeds of 2.5 to 3 mc in activity. We have seen excellent response in 9 patients. In these patients the area irradiated has shown good local control. A number of patients have had deep seated tumors which could be exposed sufficiently to allow implantation at the time of surgery. Figure 4 is a roentgenogram of an implant done 1½ years prior to this study. At surgery, metastatic lymph nodes from carcinoma of the cervix were implanted. The patient's pain was relieved and swelling of the leg decreased. Chromium 51, with its relatively long

TABLE III

QUESTIONABLE OR UNFAVORABLE RESULTS AND INSUFFICIENT TIME FOR EVALUATION

Patient	Diagnosis	Previous Treatment	No. of Chromium Seeds and Activity	Calculated Dose	Comments
R.T.	Transitional cell carcinoma of bladder	Roentgen therapy and surgery	28–2.00 mc	3,000 rads	Died of pyelonephritis and septicemia. Insufficient time to evaluate
V.M.	Squamous cell carcinoma of cheek	Surgery and roentgen therapy	25–4.00 mc	4,300 rads	Died of hemorrhage 1 month following implant
A.S.	Carcinoma of cervix with vaginal recurrence	Radium and roentgen therapy	51–4.00 mc	5,500 rads	Necrosis and tumor present at autopsy 1 month later
E.M.	Mucoepidermoid carcinoma of nasopharynx	Surgery and roentgen therapy	6–3.60 mc	6,000 rads	Normal reaction at 3 weeks. Insufficient follow-up
A.K.	Squamous cell carcinoma of posterior tongue	Roentgen therapy	29–3.50 mc	6,200 rads	Transient response of 3 months duration in tongue lesions
M.R.	Carcinoma of cervix with involvement of bladder	Roentgen therapy and radium	48–3.00 mc	5,000 rads	Necrosis of anterior vaginal wall. Marked relief of pain and decrease in infiltrates in parametrium
O.L.	Squamous cell carcinoma of buccal mucosa	Roentgen therapy	10–3.50 mc	4,500 rads	Only temporary decrease in size of neck metastases

half-life, allows us to keep a supply of radioactive chromium seeds in stock in a sterilized lead pot. Two implantation guns are available and sterilized ready for use. Those sources that decay one half-life become half strength seeds for use in implantations where a tissue dose of between 2,000 and 3,000 rads is desired. Eight of the implants have been done under local anesthesia in the out-patient clinic.

FIG. 4. A roentgenogram of an implant of a patient with recurrent carcinoma of the cervix with metastatic tumor in iliac lymph nodes.

DISCUSSION

We have found chromium 51 seeds to be very flexible and useful sources for interstitial implantation. The relatively long half-life, the absence of beta irradiation, and the ease of handling have been important features. It has been possible to keep a stock of radioactive sources constantly available, sterilized and ready for operative implantation in deep seated tumors. There has been a relatively low incidence of tissue necrosis, and in previously irradiated areas, the additional irradiation from this permanent implant has been generally well tolerated. It may be that the relatively low dose rate from these permanent implants allows the normal tissue to proliferate and repopulate the irradiated area.

We are currently using a computer program to investigate the possibilities of improving our dosimetry in these implants. The late effects of these long lived permanent interstitial implants are also being investigated.

SUMMARY

1. The clinical use of a permanent chromium 51 implantation technique is described.

2. Twenty-five patients have had 31

implants, the longest being in place for 7.5 years.

3. The fabrication, preparation, physical properties, and clinical use of these interstitial sources are described.

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THE M. D. ANDERSON METHOD FOR THE COMPUTATION OF ISODOSE CURVES AROUND INTERSTITIAL AND INTRACAVITARY RADIATION SOURCES*

I. DOSE FROM LINEAR SOURCES

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IN THE nearly 70 years that radium has been used for the treatment of malignancy, the methods of dose control have progressed toward a more detailed description of the radiation distribution as permitted by the knowledge and technology of the time. The early unit of milligram-hour reveals nothing of the dose distribution, but continues to have some usefulness as a rough indicator of patient tolerance to radiation. The Paterson-Parker system[34,35,36] and the Quimby system[39] were introduced in the early 1930s. These highly successful systems permit the calculation of a single number to represent the dose in a plane parallel to a plane of sources or the dose near the periphery of an implanted volume. The automatic computer has made possible the calculation of full isodose distributions around arrays of sources. The work of Nelson and Meurk[32] and of the authors[44,46] has been followed by a number of improvements and variants.[1,2,4,8,13,20,25,31,33,42,43,49] A new method initiated 3 years ago at this institution,[7] together with the earlier method, has been utilized routinely in calculating the dose distributions for about 300 interstitial implants and 1,500 intracavitary treatments.

The physics and mathematics of the M. D. Anderson system will be presented in a series of three papers. In this paper a review will be made of the dose expected from linear radium sources, including new tables of dose rates from various linear sources. The second paper[6] will present the mathematics of the RADCOMP computer program. This program can be utilized for linear or point sources of any isotope. No limiting assumptions are required concerning the position of the sources or the planes of calculation. Full isodose distributions are automatically plotted and labelled. In the third paper,[47] the computer input from roentgenograms and the relation of computer calculations to the Paterson-Parker calculations will be considered. A partial clinical evaluation of the usefulness of isodose distributions has appeared in an extensive retrospective study[12] in which a high correlation was demonstrated between tumor recurrence and local low dose and between necrosis and local high dose. An analysis of isodose calculations in four planes for treatment of carcinoma of the cervix has been presented.[9] Additional clinical evaluation is in progress.

At the outset of the computer method it was decided to calculate the absorbed dose in rads as accurately as possible. Accordingly, the dose delivered by filtered linear sources and the attenuation of gamma rays in tissue were considered in detail.

METHOD OF CALCULATION

There are at least two ways of computing the dose from a filtered linear source: (a) by dividing the source into a large number of point sources (interval method) and (b) by use of the Sievert integral.[45] Because of the complex gamma-ray spectrum of radium,

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the transmission of gamma rays through platinum does not decrease exponentially with the thickness of the platinum absorber and thus the absorption coefficient varies as the gamma rays traverse the platinum filter. Therefore, for radium it is more accurate to employ the interval method, utilizing experimental data for the attenuation of the gamma rays in platinum; this is the method of calculation used to obtain the linear source tables presented here. However, for regions of interest in radiation therapy, the Sievert integral is approximately equivalent to the interval method, provided the effective absorption coefficient (defined later) is properly chosen. Since the Sievert integral is more efficient for machine computation, this method is employed for routine evaluation of dose distributions around arrays of multiple sources.

ABSORPTION IN THE RADIUM SALT

The calculated dose from a radium source should be corrected to allow for the gamma-ray absorption in the radium sulfate and barium sulfate salts. For medical sources the internal diameter of the radium container is about 1 mm. and thus the absorption is small. Utilizing several methods of calculation[10,33,53] and an absorption coefficient of 0.170 cm.$^{-1}$,[3] a multiplicative correction factor of about 0.995 is obtained for medical radium sources.

EFFECTIVE WALL THICKNESS

The effective wall thickness must also be considered in calculating the dose from radium in a cylindrical container. Since the internal diameter of the needle is finite, some of the gamma rays traverse a thickness of filter greater than the radial thickness of the wall. Utilizing the method of calculation given by Evans and Evans,[10] Keyser[24] has calculated the effective wall thickness allowing for the increased thickness of wall which some gamma rays traverse (Fig. 1). The effective wall thickness, rather than the radial wall thickness,

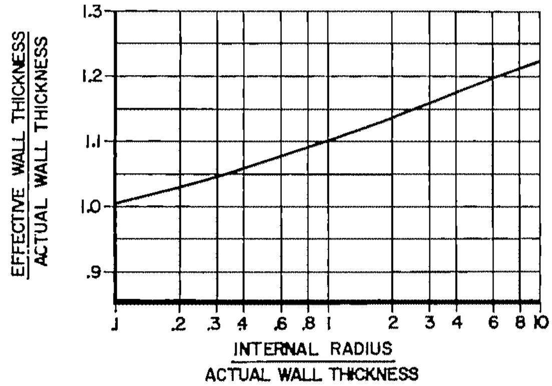

Fig. 1. Effective wall thickness of cylindrical absorbers.[24] (Reproduced by permission of the National Research Council of Canada from the *Canadian Journal of Physics*).

of the needle or tube should be employed for calculation purposes.

ABSORPTION IN PLATINUM WALL

In using the Sievert integral to calculate the dose from a filtered linear source, the term "effective absorption coefficient" is defined as an absorption coefficient which would produce the observed diminution of gamma intensity, assuming exponential absorption. The experimental transmission of radium gamma rays through platinum is given in Figure 2. In considering the dose delivered to a point from a linear radium source, the gamma rays originating at different points along the source pass through different thicknesses of platinum and thus have different effective absorp-

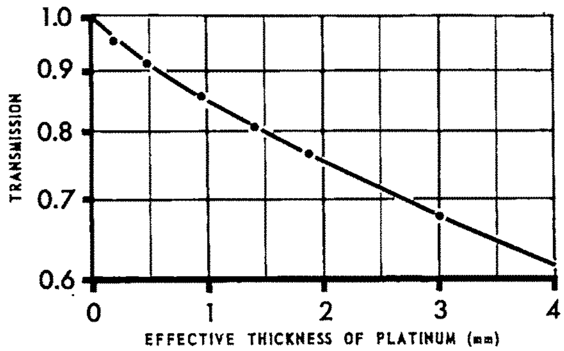

Fig. 2. Experimental transmission of gamma rays of radium in platinum.[51]

tion coefficients. Young and Batho[58] have suggested 1.52 cm.$^{-1}$ as a suitable constant value to use for points opposite the active length of a source with radial wall thickness of 0.5 mm. of platinum. The authors obtained a somewhat different value by another method: the dose to points on lines perpendicular to the center and active end of the source was calculated by dividing the source into point sources (up to 100) and allowing for the attenuation in the filter from each point according to the experimental absorption shown in Figure 2. Increasing the number of intervals altered the dose by less than 0.1 per cent. These dose rates, which were taken as correct, were then compared with those obtained by using the Sievert integral with a number of constant absorption coefficients. The best results were obtained using an absorption coefficient of 1.70 cm.$^{-1}$ for 0.5 mm. platinum filter and 1.50 cm.$^{-1}$ for 1.0 mm. platinum filter. Considering the dose rates on the perpendicular bisectors of sources with 15, 20, 30 and 40 mm. active length and on lines perpendicular to the sources at the active ends, the average error introduced by the choice of these effective absorption coefficients for use with the Sievert integral is 0.2 per cent, with a maximum error of 1.3 per cent. Beyond the active length of the source the error would be larger, with the Sievert integral calculation being too low. In the RADCOMP program the Sievert integral is employed with the above absorption coefficients.

SPECIFIC GAMMA-RAY EMISSION

The determination of the ionization produced in a given volume of air by a stated weight of radium element is a problem of considerable experimental difficulty which has received attention over a number of years. Mayneord and Roberts[27] determined the specific gamma-ray emission (Γ factor) for a point source of radium filtered by 0.5 mm. of platinum to be 8.3 r-cm.^{2}/mg.-hr. Other early values varied from 7.8 to 8.9 r-cm.^{2}/mg.-hr.[11,14,16,23,26] The Paterson-Parker tables were based on the value 8.4 r-cm.^{2}/mg.-hr. A recent determination by Attix and Ritz[8] has yielded a value of 8.26 r-cm.^{2}/mg.-hr. for radium filtered by 0.5 mm. of platinum, which is in good agreement with the value published by Mayneord and Roberts.[27] The International Commission on Radiological Units and Measurements[22] has recommended that the specific gamma-ray emission of radium filtered by 0.5 mm. of platinum be taken as 8.25 r-cm.^{2}/mg.-hr.[15] The Γ factors for radium with other thicknesses of platinum filter given in Table I are based on 8.25 r-cm.^{2}/mg.-hr. for 0.5 mm. of platinum and on ratios to other thicknesses of platinum determined by using the data given in Figure 2.

EFFECT OF CELLULARITY

In calculating the dose distribution from a radium needle, it is usual to ignore the cellular construction and consider the source as being uniformly loaded. The magnitude of the error introduced by this approximation is small, as seen in Figure 3. At a distance of 0.5 cm. from the needle the isodensity patterns are almost the same for cellular and continuous sources, assuming a separation of 1 mm.

TABLE I

SPECIFIC GAMMA-RAY EMISSION (Γ FACTOR) FOR RADIUM POINT SOURCE FILTERED BY VARIOUS THICKNESSES OF PLATINUM

Filter (mm. Pt)	Γ Factor $\left(\frac{\text{r-cm.}^2}{\text{mg.-hr.}}\right)$*
0	9.09
0.5	8.25
0.6	8.14
0.7	8.01
0.8	7.90
0.9	7.81
1.0	7.71
1.5	7.25
2.0	6.84

* These Γ factors are based upon the experimentally determined Γ factor at 0.5 mm. platinum filtration[22] with the Γ factors for other thicknesses of platinum filtration derived by ratios to that at 0.5 mm. platinum determined from Figure 2.

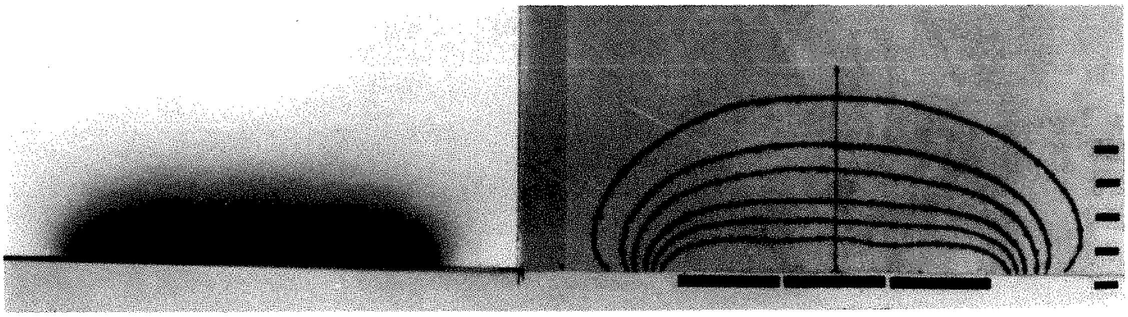

Fig. 3. Autoradiograph and plot of isodensity lines showing effect of cellularity in a 4.5 cm. active length radium needle (3 cell loading). Cell separation is about 1 mm. Markings at the right indicate 0.5 cm. intervals from the center of the needle.

between cells. Modern radium sources are manufactured to have 1 mm. separation between the radioactivity in the cells, although a separation of 2 mm. is seen occasionally in older radium needles.

ATTENUATION OF GAMMA RAYS

In addition to gamma-ray absorption in the radium salt and the platinum container, there is gamma-ray attenuation in tissue, which is taken to be the same as that in water. Experimental determinations of the changes in radiation dose in water compared with the dose in air have been made at various distances from sources of radium, cobalt 60, cesium 137, and iridium 192.[18,19,30,37,41,48,50,52] Theoretical calculations of the diffusion of gamma rays through a scattering medium are consistent with experimental determinations.[21,28]

For radium sources there is a reduction of about 1 per cent per 1 cm. for intervening tissue up to 4 cm. from the source. A more precise description of the effective absorption of gamma rays from point sources in tissue is given by the following empirical equation:

$$\frac{\text{Exposure in water}}{\text{Exposure in air}} = A + Br + Cr^2 + Dr^3, \quad (1)$$

where

r = perpendicular distance in centimeters.

The coefficients A, B, C, and D for Equation 1 are listed in Table II for gold 198, iridium 192, cesium 137, radium 226, and cobalt 60.[28]

LINEAR SOURCE TABLES

Tables of the dose rates from filtered radium sources of various lengths have been published.[17,29,40,53] The parameters used in earlier calculations and by the authors appear in Table III. In each case the specific gamma-ray emission from unfiltered radium was obtained by calculating to zero platinum thickness with the absorption coefficient and specific gamma-ray

Table II

COEFFICIENTS FOR EQUATION 1 TO CALCULATE THE ATTENUATION OF GAMMA RAYS IN WATER[28]

Isotopes	A	B	C	D
Au^{198}	1.0306×10^{0}	-8.134×10^{-3}	1.111×10^{-3}	-1.597×10^{-4}
Ir^{192}	1.0128×10^{0}	5.019×10^{-3}	-1.178×10^{-3}	-2.008×10^{-5}
Cs^{137}	1.0091×10^{0}	-9.015×10^{-3}	-3.459×10^{-4}	-2.817×10^{-5}
Ra^{226}	1.0005×10^{0}	-4.423×10^{-3}	-1.707×10^{-3}	7.448×10^{-5}
Co^{60}	9.9423×10^{-1}	-5.318×10^{-3}	-2.610×10^{-3}	1.327×10^{-4}

TABLE III

FACTORS EMPLOYED IN THE CALCULATION OF DOSES FROM LINEAR RADIUM SOURCES

	Paterson and Parker[29] (Sievert integral)	Greenfield *et al.*[17] (Sievert integral)	Young and Batho[33] (Sievert integral)	Authors: RADCOMP (Sievert integral)	Authors: Linear Source Table (intervals)
1. Γ factor (no filtration), r-cm.²/mg.-hr.	9.3	9.33	9.08	9.09	9.09
2. Γ factor (0.5 mm. Pt), r-cm.²/mg.-hr.	8.4	8.4	8.25	8.25	8.25
3. Attenuation in radium salt	—	0.15 cm.⁻¹	Included in "effective wall thickness"	0.995	0.995
4. Effective thickness Pt					
0.5 mm. Pt (nominal), mm.	—	—	0.56–0.579	0.541	0.541
1.0 mm. Pt (nominal), mm.	—	—	1.067–1.175	1.080	1.080
5. Absorption in platinum					
0.5 mm. Pt	2.0 cm.⁻¹	2.0 cm.⁻¹	Variable	1.70 cm.⁻¹	Experimental data
1.0 mm. Pt	2.0 cm.⁻¹	1.94 cm.⁻¹	Variable	1.50 cm.⁻¹	Experimental data
6. Attenuation in tissue	—	—	Equation based on experimental data[5]	Polynomial based on experimental data	Polynomial based on experimental data
7. Units	mg.-hr./1,000 r	r/mg.-hr.	rads/mg.-hr.	rads/mg.-hr.	rads/mg.-hr.
8. rads/roentgen	—	—	0.97	0.957	0.957
9. Multiplicative factor to obtain rads	0.94*	0.94*	~0.99	~1.00	1.00

* Minus 1 per cent per cm. for tissue absorption to 4 cm.

emission appropriate for 0.5 mm. platinum. New linear source calculations which take into account presently known factors are listed in Table IV. These data were computed by dividing the sources into 40 intervals and allowing for the experimental attenuation in platinum (Fig. 2) and in tissue (Equation 1). The dose rates are given in terms of rads per hour per milligram in muscle for radium gamma rays at various points around sources of the type commonly utilized in therapy.

TABLE IVA

RADS PER MILLIGRAM-HOUR IN TISSUE DELIVERED AT VARIOUS DISTANCES BY LINEAR RADIUM SOURCES FILTRATION = 0.5 MM. PLATINUM

(Dose rates are omitted where γ rays traverse more than 7 mm. Pt)

Perpendicular Distance from Source (cm.)	Distance Along Source Axis (cm. from center): 0	0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5.0
	Active Length 1.5 cm.										
0.25	50.67	43.75	11.94	3.34	1.48	.81	.50	—	—	—	—
0.5	20.26	16.95	8.18	3.38	1.70	1.00	.64	.44	.31	.23	.18
0.75	10.84	9.29	5.67	2.99	1.67	1.03	.69	.48	.35	.27	.21
1.0	6.67	5.89	4.10	2.52	1.55	1.01	.69	.50	.37	.28	.22
1.5	3.20	2.96	2.38	1.74	1.24	.89	.65	.48	.37	.29	.23
2.0	1.85	1.76	1.52	1.23	.96	.74	.57	.45	.35	.28	.23
2.5	1.20	1.15	1.04	.89	.74	.60	.49	.40	.32	.26	.22
3.0	.83	.81	.75	.67	.58	.49	.41	.34	.29	.24	.21
3.5	.61	.60	.57	.52	.46	.40	.35	.30	.26	.22	.19
4.0	.47	.46	.44	.41	.37	.33	.29	.26	.23	.20	.17
4.5	.37	.36	.35	.33	.30	.28	.25	.22	.20	.18	.16
5.0	.30	.29	.28	.27	.25	.23	.21	.19	.17	.16	.14

TABLE IVA (*Continued*)

Perpendicular Distance from Source (cm.)	Distance Along Source Axis (cm. from center) 0	0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5.0
					Active Length 2.0 cm.						
0.25	39.99	37.99	21.38	4.57	1.75	.90	.54	—	—	—	—
0.5	17.01	15.59	9.97	4.15	1.94	1.09	.68	.46	.33	.24	.18
0.75	9.56	8.71	6.14	3.38	1.85	1.11	.72	.50	.37	.27	.21
1.0	6.09	5.59	4.23	2.71	1.67	1.07	.72	.51	.38	.29	.23
1.5	3.04	2.85	2.37	1.79	1.29	.92	.67	.50	.38	.30	.24
2.0	1.79	1.71	1.51	1.24	.97	.75	.58	.45	.36	.29	.23
2.5	1.17	1.13	1.03	.89	.75	.61	.49	.40	.33	.27	.22
3.0	.82	.80	.75	.67	.58	.49	.42	.35	.29	.25	.21
3.5	.60	.59	.56	.51	.46	.40	.35	.30	.26	.22	.19
4.0	.46	.46	.44	.41	.37	.33	.29	.26	.23	.20	.17
4.5	.36	.36	.35	.33	.30	.28	.25	.22	.20	.18	.16
5.0	.29	.29	.28	.27	.25	.23	.21	.19	.17	.16	.14
					Active Length 2.5 cm.						
0.25	32.92	32.16	27.00	7.56	2.24	1.04	.60	—	—	—	—
0.5	14.54	13.89	11.01	5.39	2.33	1.22	.74	.49	.34	.25	.19
0.75	8.46	8.00	6.39	3.89	2.11	1.22	.78	.53	.38	.28	.22
1.0	5.54	5.23	4.28	2.94	1.83	1.16	.77	.54	.40	.30	.23
1.5	2.86	2.73	2.35	1.83	1.34	.96	.70	.52	.39	.30	.24
2.0	1.72	1.66	1.48	1.24	.99	.77	.60	.47	.37	.29	.24
2.5	1.14	1.11	1.02	.89	.75	.62	.50	.41	.33	.27	.23
3.0	.80	.79	.74	.66	.58	.50	.42	.35	.30	.25	.21
3.5	.60	.58	.56	.51	.46	.40	.35	.30	.26	.22	.19
4.0	.46	.45	.43	.40	.37	.33	.30	.26	.23	.20	.17
4.5	.36	.36	.34	.33	.30	.28	.25	.22	.20	.18	.16
5.0	.29	.29	.28	.27	.25	.23	.21	.19	.18	.16	.14
					Active Length 3.0 cm.						
0.25	27.93	27.58	25.77	14.50	3.20	1.28	—	—	—	—	—
0.5	12.64	12.32	10.91	6.96	2.97	1.43	.83	.53	.36	.26	.20
0.75	7.54	7.28	6.33	4.42	2.47	1.39	.85	.57	.40	.30	.23
1.0	5.04	4.85	4.22	3.14	2.03	1.28	.83	.57	.42	.31	.24
1.5	2.69	2.59	2.30	1.87	1.40	1.02	.73	.54	.41	.31	.25
2.0	1.65	1.60	1.46	1.25	1.01	.80	.62	.48	.38	.30	.24
2.5	1.11	1.08	1.00	.89	.76	.63	.51	.42	.34	.28	.23
3.0	.79	.77	.73	.66	.58	.50	.42	.36	.30	.25	.21
3.5	.58	.58	.55	.51	.46	.41	.35	.31	.26	.23	.19
4.0	.45	.44	.43	.40	.37	.33	.30	.26	.23	.20	.18
4.5	.36	.35	.34	.32	.30	.28	.25	.23	.20	.18	.16
5.0	.29	.29	.28	.27	.25	.23	.21	.19	.18	.16	.14
					Active Length 3.5 cm.						
0.25	24.22	24.05	23.25	19.45	5.51	1.68	—	—	—	—	—
0.5	11.16	10.98	10.26	8.08	3.99	1.77	.95	.59	.39	.28	.21
0.75	6.78	6.63	6.06	4.79	2.94	1.62	.96	.62	.43	.31	.24
1.0	4.61	4.49	4.07	3.28	2.26	1.43	.92	.62	.44	.33	.25
1.5	2.53	2.46	2.24	1.89	1.47	1.08	.78	.57	.43	.33	.26
2.0	1.58	1.54	1.42	1.24	1.03	.82	.64	.50	.39	.31	.25
2.5	1.07	1.05	.98	.88	.76	.64	.52	.43	.35	.29	.24

Table IVA (*Continued*)

Perpendicular Distance from Source (cm.)	Distance Along Source Axis (cm. from center)										
	0	0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5.0
	Active Length 3.5 cm.										
3.0	.77	.75	.71	.65	.58	.50	.43	.36	.31	.26	.22
3.5	.57	.57	.54	.50	.46	.41	.36	.31	.27	.23	.20
4.0	.44	.44	.42	.40	.37	.33	.30	.26	.23	.20	.18
4.5	.35	.35	.34	.32	.30	.28	.25	.23	.20	.18	.16
5.0	.29	.28	.28	.26	.25	.23	.21	.19	.18	.16	.14
	Active Length 4.0 cm.										
0.25	21.38	21.28	20.87	19.44	10.96	—	—	—	—	—	—
0.5	9.97	9.87	9.48	8.34	5.33	2.31	1.13	.66	.43	.30	.22
0.75	6.14	6.05	5.71	4.91	3.43	1.94	1.11	.69	.47	.33	.25
1.0	4.23	4.15	3.88	3.33	2.48	1.61	1.03	.68	.48	.35	.26
1.5	2.37	2.32	2.16	1.89	1.52	1.14	.83	.61	.45	.34	.27
2.0	1.51	1.47	1.38	1.23	1.04	.85	.67	.52	.41	.32	.26
2.5	1.03	1.01	.96	.87	.76	.65	.54	.44	.36	.29	.24
3.0	.75	.73	.70	.65	.58	.51	.44	.37	.31	.26	.22
3.5	.56	.55	.53	.50	.46	.41	.36	.31	.27	.23	.20
4.0	.44	.43	.42	.39	.37	.33	.30	.27	.23	.21	.18
4.5	.35	.34	.33	.32	.30	.28	.25	.23	.20	.18	.16
5.0	.28	.28	.27	.26	.25	.23	.21	.20	.18	.16	.14
	Active Length 4.5 cm.										
0.25	19.12	19.06	18.83	—	—	—	—	—	—	—	—
0.5	9.01	8.95	8.71	8.09	6.36	3.16	1.42	.77	.48	.33	.24
0.75	5.60	5.54	5.33	4.84	3.81	2.35	1.31	.79	.52	.36	.27
1.0	3.90	3.85	3.67	3.29	2.65	1.83	1.16	.76	.52	.37	.28
1.5	2.23	2.19	2.07	1.86	1.56	1.21	.89	.65	.48	.36	.28
2.0	1.44	1.41	1.34	1.22	1.05	.87	.69	.54	.43	.34	.27
2.5	.99	.98	.93	.86	.76	.66	.55	.45	.37	.30	.25
3.0	.72	.71	.69	.64	.58	.51	.44	.38	.32	.27	.23
3.5	.55	.54	.52	.49	.45	.41	.36	.32	.27	.24	.20
4.0	.43	.42	.41	.39	.36	.33	.30	.27	.24	.21	.18
4.5	.34	.34	.33	.32	.30	.27	.25	.23	.20	.18	.16
5.0	.28	.28	.27	.26	.25	.23	.21	.20	.18	.16	.14
	Active Length 5.0 cm.										
0.25	17.29	17.25	—	—	—	—	—	—	—	—	—
0.5	8.21	8.17	8.02	7.66	6.73	4.31	1.88	.93	.55	—	—
0.75	5.15	5.11	4.97	4.66	4.00	2.80	1.59	.92	.58	.40	.29
1.0	3.62	3.58	3.45	3.20	2.74	2.04	1.33	.86	.57	.40	.30
1.5	2.10	2.07	1.98	1.82	1.58	1.27	.96	.70	.52	.39	.30
2.0	1.37	1.35	1.29	1.19	1.06	.89	.72	.57	.45	.35	.28
2.5	.96	.94	.91	.84	.76	.66	.56	.47	.38	.31	.26
3.0	.70	.69	.67	.63	.58	.51	.45	.38	.33	.27	.23
3.5	.54	.53	.51	.49	.45	.41	.36	.32	.28	.24	.21
4.0	.42	.42	.40	.38	.36	.33	.30	.27	.24	.21	.18
4.5	.34	.33	.32	.31	.29	.27	.25	.23	.21	.18	.16
5.0	.27	.27	.27	.26	.24	.23	.21	.20	.18	.16	.15

TABLE IVB

RADS PER MILLIGRAM-HOUR IN TISSUE DELIVERED AT VARIOUS DISTANCES BY LINEAR RADIUM SOURCES
FILTRATION = 1.0 MM. PLATINUM

(Dose rates are omitted where γ rays traverse more than 7 mm. Pt)

Perpendicular Distance from Source (cm.)	Distance Along Source Axis (cm. from center)										
	0	0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5.0
	Active Length 1.0 cm.										
0.25	62.10	36.03	6.45	—	—	—	—	—	—	—	—
0.5	22.57	15.50	5.88	2.48	1.26	.73	.46	—	—	—	—
0.75	11.37	8.78	4.62	2.36	1.32	.81	.53	.37	.26	.20	.16
1.0	6.75	5.62	3.56	2.09	1.28	.82	.56	.40	.29	.22	.17
1.5	3.12	2.83	2.17	1.53	1.07	.76	.55	.41	.31	.24	.19
2.0	1.78	1.67	1.41	1.11	.85	.64	.49	.38	.30	.24	.19
2.5	1.14	1.09	.97	.82	.67	.53	.43	.34	.28	.23	.19
3.0	.79	.77	.71	.62	.53	.44	.37	.30	.25	.21	.18
3.5	.58	.57	.53	.48	.42	.37	.31	.27	.23	.19	.16
4.0	.44	.43	.41	.38	.34	.30	.27	.23	.20	.17	.15
4.5	.35	.34	.33	.31	.28	.26	.23	.20	.18	.16	.14
5.0	.28	.27	.27	.25	.24	.22	.20	.18	.16	.14	.13
	Active Length 1.5 cm.										
0.25	45.87	39.70	10.19	—	—	—	—	—	—	—	—
0.5	18.56	15.51	7.25	2.88	1.39	.78	.49	—	—	—	—
0.75	10.01	8.54	5.10	2.60	1.43	.86	.56	.38	.27	.20	.16
1.0	6.20	5.44	3.72	2.23	1.35	.86	.58	.41	.30	.22	.17
1.5	2.99	2.75	2.18	1.57	1.10	.78	.56	.41	.31	.24	.19
2.0	1.73	1.64	1.40	1.12	.86	.65	.50	.39	.30	.24	.20
2.5	1.12	1.08	.97	.82	.67	.54	.43	.35	.28	.23	.19
3.0	.78	.76	.70	.62	.53	.44	.37	.31	.26	.21	.18
3.5	.57	.56	.53	.48	.42	.37	.31	.27	.23	.19	.17
4.0	.44	.43	.41	.38	.34	.31	.27	.23	.20	.17	.15
4.5	.34	.34	.33	.31	.28	.26	.23	.20	.18	.16	.14
5.0	.28	.27	.26	.25	.23	.22	.20	.18	.16	.14	.13
	Active Length 2.0 cm.										
0.25	36.04	34.29	—	—	—	—	—	—	—	—	—
0.5	15.50	14.23	8.99	3.57	1.60	.86	.53	—	—	—	—
0.75	8.78	8.00	5.57	2.97	1.59	.93	.59	.40	.28	.21	.16
1.0	5.62	5.15	3.86	2.42	1.46	.92	.61	.43	.31	.23	.18
1.5	2.83	2.65	2.18	1.62	1.14	.81	.58	.43	.32	.25	.20
2.0	1.67	1.59	1.39	1.13	.88	.67	.51	.40	.31	.25	.20
2.5	1.09	1.06	.96	.82	.68	.55	.44	.35	.29	.23	.19
3.0	.77	.75	.69	.62	.53	.45	.37	.31	.26	.22	.18
3.5	.57	.55	.52	.48	.42	.37	.32	.27	.23	.20	.17
4.0	.43	.43	.41	.38	.34	.31	.27	.23	.20	.18	.15
4.5	.34	.34	.32	.31	.28	.26	.23	.20	.18	.16	.14
5.0	.27	.27	.26	.25	.23	.22	.20	.18	.16	.14	.13

When corrected to absorbed dose, the specific gamma-ray emission of 8.25 r-cm.^{2}/mg.-hr., and for tissue absorption, the Paterson-Parker,[29] the Greenfield *et al.*,[17] and the authors' tables for linear sources agree to within about 1 per cent for filtrations of 0.5 mm. platinum in regions opposite the active length. However, due to the choice of absorption coefficients employed in the Sievert integral for sources with 1 mm. platinum filtration, differences of up to 11 per cent at 0.5 cm. from the sources and 3 per cent at 1 cm. and beyond are noted with the Paterson-Parker tables (with allowance for change in the specific gamma-ray emission, tissue attenuation, and absorbed dose). Differences of 3 to 4 per cent are noted with the Greenfield *et al.*,[17] tables in regions opposite the active length and much larger differences beyond the active ends. The dose rates in the tables presented here are higher than in both of these tables. As pointed out by Greenfield *et al.*,[17] there are inconsistencies in the Quimby tables[40] which have also been noted by the authors.

The tables by Young and Batho[53] give the dose rates in considerable detail and may be applied to sources of any length. These tables and the authors' tables agree to within about 1 per cent at both 0.5 mm. platinum and 1.0 mm. platinum filtration opposite the active length and to within a few per cent beyond the active ends. The agreement is not surprising since the tables are based upon the same experimental attenuation of gamma rays in platinum; the Young and Batho method, however, employs an additional step of deriving a variable absorption coefficient to be used with the Sievert integral.

SUMMARY

A review of the physical factors that are used to compute the dose in rads at points around linear radium sources has included a consideration of the gamma-ray absorption in the radioactive source and the container, the effect of cellularity in the source construction, and the effective absorption coefficients for use with the Sievert integral.

The effective attenuation in tissue of the gamma rays of gold 198, iridium 192, cesium 137, radium 226, and cobalt 60 have been considered.

In addition, new tables based upon recent experimental data are given for the radiation dose around linear radium sources.

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vision. The approximation remains good in the case that μ^1 depends on r; the error estimates given above may not hold since r^* is changed, but for the usual situations encountered in practice, this does not appear to be the case.

In calculating the dose on a plane rectangular grid, a considerable amount of work can be saved by arranging the calculations so that the appropriate values of X_1, X_2 and Y_0 can be obtained incrementally; this can be done even if the plane does not contain the source. Extraction of roots can be eliminated by storing a table of $\exp(-\mu^1 r)$ versus r^2 for the table lookup.

LOCATION OF SOURCES FROM STEREO-ROENTGENOGRAMS

Source locations are usually determined by measurements on roentgenograms. Procedures frequently used depend on accurate positioning of roentgen-ray equipment relative to the films. The present program reduces the possibility of error in such procedures by determining the relative positions of the stereo-roentgenograms and the roentgen-ray tube directly from projections of fiducial points on the roentgenograms. Details of the method are given in a report which is available from the author.[2]

Consider a set of points $P_i=(p_{i1},p_{i2},p_{i3})$, $i=1, 2, \cdots, n$, which we shall call the fiducial points. Suppose that the roentgen-ray source is located at $S=(s_1,s_2,s_3)$. We shall assume that the points P_i represent the centers of radiopaque spheres whose images appear on the roentgenograms. Assume further that the film lies in the plane $[(X,Y,-d)]$, where d is some fixed number which we assume to be negative (as in the case that the origin of the coordinates lies on the surface of the roentgenographic table and the film is held beneath the table). Let $P_i'=(p_{i1}',p_{i2}',p_{i3}')$ denote the location of the projection (image) of P_i onto the film; then

$$p_{i3}' = -d, \qquad i = 1, \cdots, n,$$

and we have

$$P_i' = \lambda_i S + (1-\lambda_i)P_i, \qquad i = 1, \cdots, n,$$

where

$$\lambda_i = \frac{p_{i3} + d}{p_{i3} - S_3}.$$

Now assume that the coordinates of the points P_i' are measured with respect to an origin O' on the roentgenogram, and that the O' coordinates are parallel to the O coordinates, but that the first two coordinates have been shifted by an amount α and β, respectively, so that the O' coordinates of P_i' are $(p_i'{}_1+\alpha, p_i'{}_2+\beta, 0)$.

Let p_{i1}^* and p_{i2}^* be the measured values of $p_{i1}'+\alpha$ and $p_{i2}'+\beta$, respectively, in the O' coordinates. Let ϵ_{i1} and ϵ_{i2}, the errors in the measurements of the coordinates, be defined by

$$\epsilon_{i1} = p_{i1}^* - p_{i1}' - \alpha,$$
$$\epsilon_{i2} = p_{i2}^* - p_{i2}' - \beta, \qquad i = 1, 2, \cdots, n.$$

The program determines α, β, S_1, S_2, and S_3 which minimize the square error

$$\sum_{i=1}^{n} [\epsilon_{i1}^2 + \epsilon_{i2}^2].$$

Small errors in orientation of the coordinates are corrected by a similar least squares estimation of the angle of rotation prior to the determination of α, β, S_1, S_2, and S_3. Thus, each pair of roentgenograms contains enough information to completely determine the positions of the films and the roentgen-ray source, thereby eliminating the need for precise positioning during roentgenography.

Once the locations of the roentgen-ray source are known, the determination of the locations of points from images on two or more roentgenograms is rather straightforward except that the effect of small errors must be taken into account. For point sources the optimum location is at the midpoint of the shortest line segment joining the lines of projection onto the images. For linear sources the same method can be

used but it is also possible to improve the estimates by making use of the known length of the source.

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THE M. D. ANDERSON METHOD FOR THE COMPUTATION OF ISODOSE CURVES AROUND INTERSTITIAL AND INTRACAVITARY RADIATION SOURCES*

III. ROENTGENOGRAMS FOR INPUT DATA AND THE RELATION OF ISODOSE CALCULATIONS TO THE PATERSON-PARKER SYSTEM

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THE computer program described here, called RADCOMP, was designed to calculate radiation distributions around multiple radioactive sources in individual treatments. A computer of the CDC 1604 or IBM 7094 capability is required. The features of the program and its application in routine dosimetry of interstitial and intracavitary implants as well as the relationship between the full isodose distributions and the Paterson-Parker system will be considered. The first paper in this series[15] gives the data used as the basis for the calculations and the second paper in this series[1] presents the mathematical aspects of the method and the computer technique utilized for computation.

An electronic computer was first used for interstitial dosimetry in this institution in 1960[13,17] employing a program which offered many advantages over manual calculations but had some limitations: in the earlier program all needles were considered to be parallel or perpendicular to each other and to the planes of calculation; the types of sources were restricted to those for which extensive tables had been computed previously; and isodose curves were simulated by grid patterns from a printer.

FEATURES OF THE COMPUTER PROGRAM (RADCOMP)

In developing RADCOMP, considerable effort was directed toward producing a general program which would accept input data with no serious restrictions on the specification of types and locations of sources. As a result, the versatility of RADCOMP represents a significant improvement over the computer method used previously. The principal features of RADCOMP are outlined below; for details concerning the program the reader is referred to Paper II of this series[1] and a user's manual which is available from the authors.

TYPES OF SOURCES

Since all calculations are done at object time, there are no restrictions concerning the types of sources used; these may be seeds, needles, or tubes with radium or any other isotope as the radioactive element. Dimensions, such as active length, physical length, and filter thickness, may be chosen arbitrarily, as well as values for the activity, the specific gamma-ray emission and the filter absorption coefficient. The data which are used for routine calculations in this institution are given in Paper I.[15]

PLANES OF CALCULATION AND LOCATION OF SOURCES

A plane of calculation may lie at any angle to the sources and may intersect the sources or be located at any distance from them. Each source is considered individually and is not required to be parallel or perpendicular to other sources. If several

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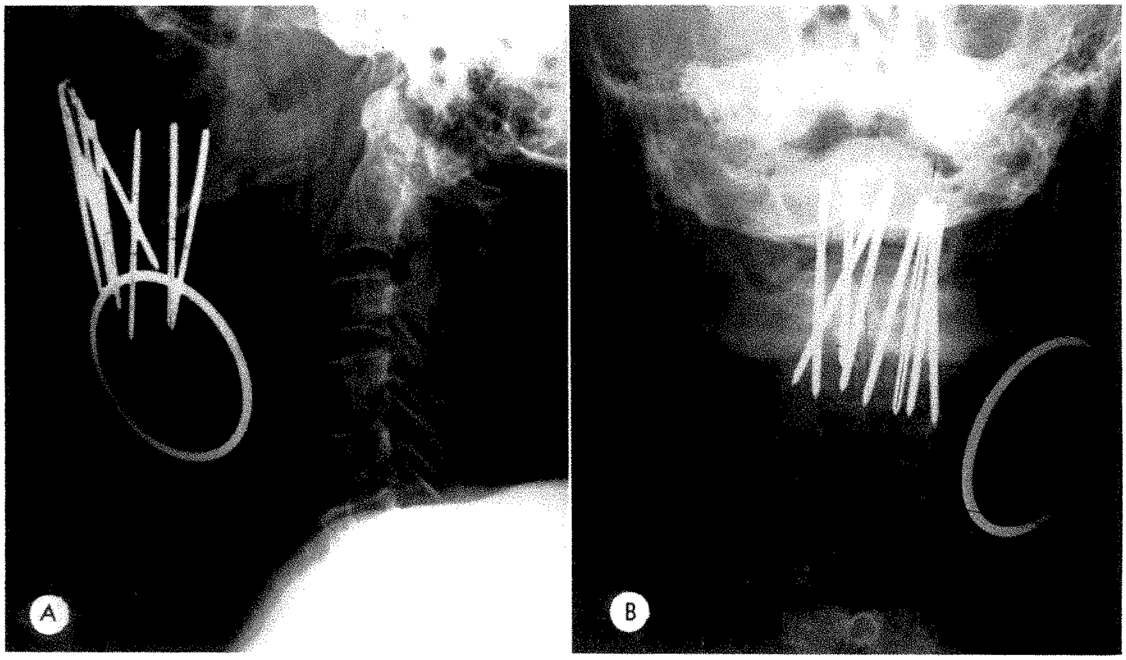


FIG. 1. (*A*) Lateral and (*B*) anteroposterior roentgenograms of an interstitial radium implant of the latera. border of the tongue. The implant is composed of 8 Indian-club needles, 1.66 mg. radium each, 4.0 cml active length, 0.65 mm. platinum filtration.

planes of calculation are desired, these may lie at any angle to each other without transformation of the coordinate system by human effort. For each plane, the over-all dimensions and distance between points of calculation (grid size) are both variables which are selected according to the type of treatment and region of interest.

METHOD OF CALCULATION

For each plane of calculation the dose rates from all sources are computed and summed for points on a grid. Dose rates from linear sources are evaluated using the Sievert integral;[16] seeds are considered as point sources by using the inverse square law. For both types of sources, an empirical polynomial[9] is used to calculate the attenuation of the gamma rays in tissue with polynomial coefficients suitable for various isotopes. All of the factors required for calculation are listed in Paper I.

OUTPUT DATA

An incremental plotter automatically draws and labels the isodose curves and plots the projection of the sources onto the plane of calculation. These graphic output data may be drawn actual size or to any degree of magnification. In addition to isodose curves, a tabular listing of dose rates on the grid of points can be obtained, although this listing is rarely useful for routine dosimetry.

USE OF ROENTGENOGRAMS TO DERIVE INPUT DATA

Since individual dose computation is based on the actual implant, rather than the planned implant, sources are localized by roentgenography. RADCOMP allows input data to be derived from either of two sets of films: orthogonal roentgenograms or stereo-roentgenograms. Both types of films have been used for many years in manual methods of dose assessment and the details of deriving the geometry of implants from films has been discussed.[14]

ORTHOGONAL ROENTGENOGRAMS

The program input includes the location of the sources by specifying their x, y, and z

coordinates in a Cartesian coordinate system. In working from orthogonal roentgenograms it is convenient to make the reference plane parallel or perpendicular to one of the roentgenograms; the three distances can then be measured directly on the films. A plane of calculation is defined by specifying 3 points, identified in both roentgenograms, through which the plane passes.

Example 1: The roentgenograms of an interstitial radium implant of the lateral border of the tongue are shown in Figure 1, *A* and *B* and the dose distribution in a midplane perpendicular to the average direction of the needles is shown in Figure 2. Usually, 1 to 3 planes of calculation are requested for an interstitial implant.

Example 2: The roentgenograms of an intracavitary radium application to the uterine cervix are shown in Figure 3, *A* and *B*. Dose distributions for this application are shown in Figure 4, *A*, *B* and *C*. Plane 1 (Fig. 4*A*) passes through the centers of the vaginal ovoids and through the internal os. Plane 2 (Fig. 4*B*) is a sagittal plane passing approximately through the axis of the uterine tandem. Plane 3 (Fig. 4*C*) passes through the pelvic brim.

STEREO-ROENTGENOGRAMS

For most cases, input data can be derived from orthogonal roentgenograms with sufficient convenience and accuracy. However, for implants in which one has difficulty matching the images of individual sources on orthogonal roentgenograms, as is usual with seed implants, it is desirable to have the option of using stereo-roentgenograms for localization.

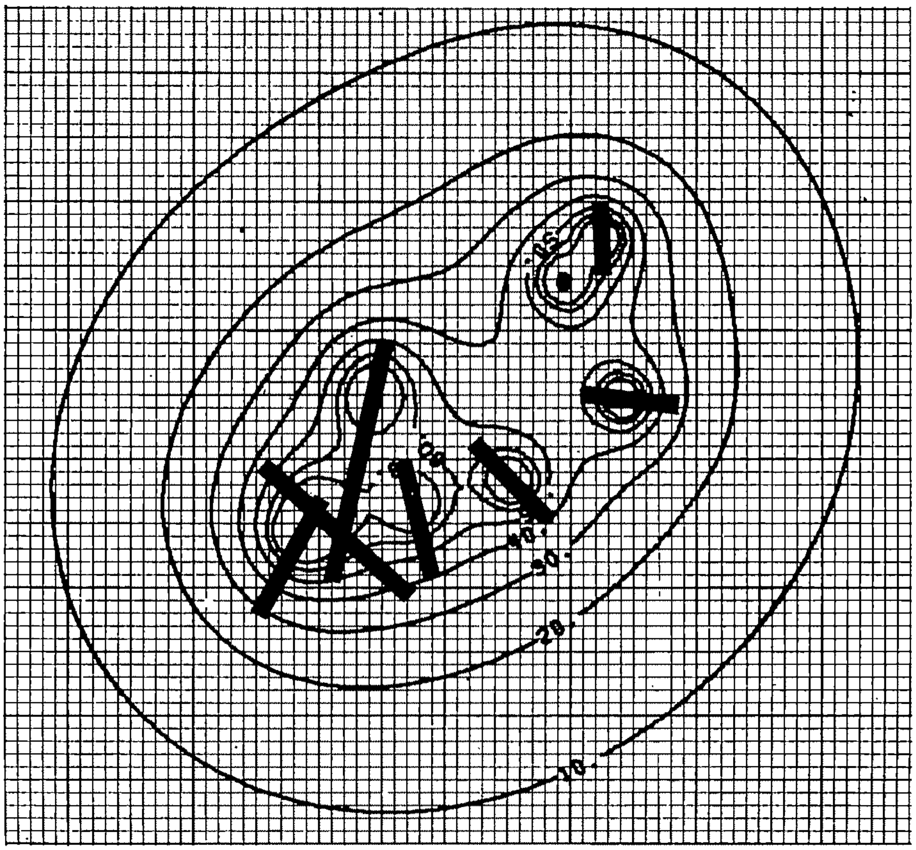


Fig. 2. Isodose curves in a plane bisecting the needles shown in Figure 1. A 1 mm. grid is in the background. The units are rads per hour.

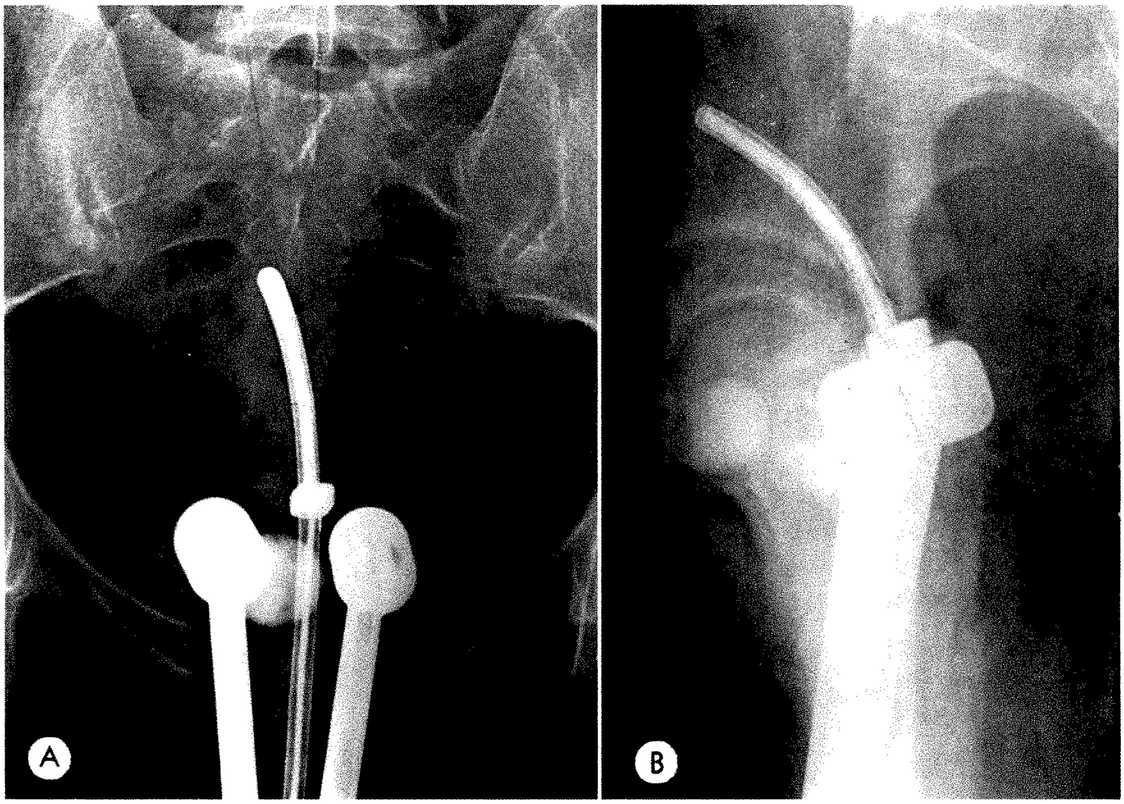


FIG. 3. (*A*) Anteroposterior and (*B*) lateral roentgenograms of an intracavitary implant of Fletcher cervical applicators. The applicators are loaded with 15+10+10 mg. radium tubes in the uterine tandem and 20+20 mg. radium tubes in the vaginal colpostats. The sources are 1.5 cm. active length with 1.0 mm. platinum filtration.

For use with the RADCOMP program, stereo-roentgenograms are taken using the special equipment shown in Figure 5. A plate beneath the patient is embedded with 8 lead shot which delimit a 20×20 cm. square. Attached to this plate is a plastic arm which contains 4 lead shot rigidly positioned in a plane parallel to the plate with a separation of 30 cm. between the 2 sets of lead shot. The images of the 12 shot are projected onto both stereo-roentgenograms and constitute "fiducial points" which indicate the geometric factors used in taking the roentgenograms and form a frame of reference for localization of the sources. A target-film distance of 100 cm. and a tube shift of 20 cm. are normally used but these distances are not critical since the actual distances are computed using the locations of the "fiducial points."

The locations of the images of the sources and the "fiducial points" in both roentgenograms are specified by measuring their locations in a two-dimensional Cartesian coordinate system. It is not necessary to make allowance for magnification of the images. From these data, the computer calculates the actual locations of the sources in space. The basis of the calculation is similar to that used for three-dimensional reconstruction.[14]

A plane of calculation is defined by specifying the locations of 3 points through which it passes; these points may be any points which can be located in the 2 roentgenograms, such as anatomic landmarks or sources.

Example 3: Stereo-roentgenograms of a gold 198 seed implant are shown in Figure 6, *A* and *B*. The dose distribution was

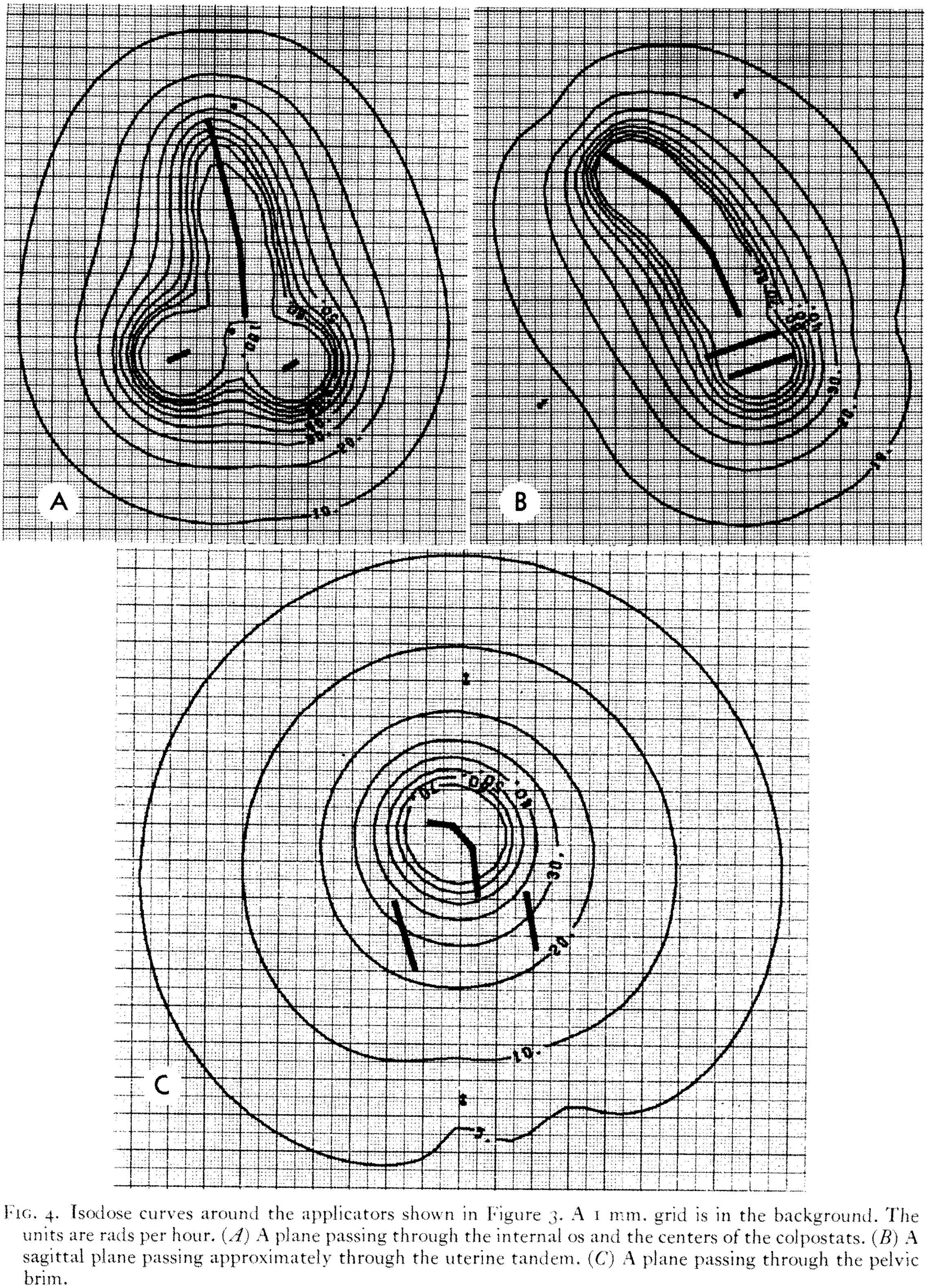


Fig. 4. Isodose curves around the applicators shown in Figure 3. A 1 mm. grid is in the background. The units are rads per hour. (*A*) A plane passing through the internal os and the centers of the colpostats. (*B*) A sagittal plane passing approximately through the uterine tandem. (*C*) A plane passing through the pelvic brim.

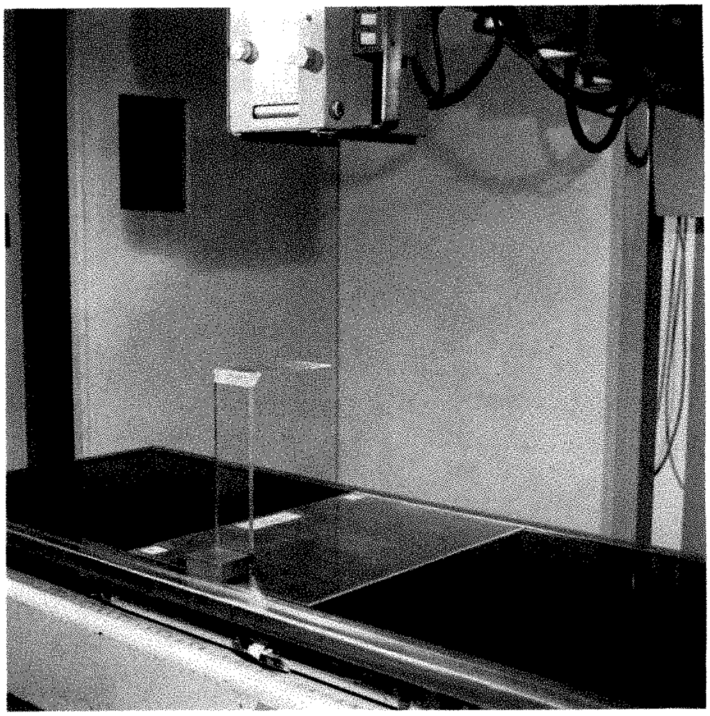


Fig. 5. Equipment used to project "fiducial points" onto stereo-roentgenograms.

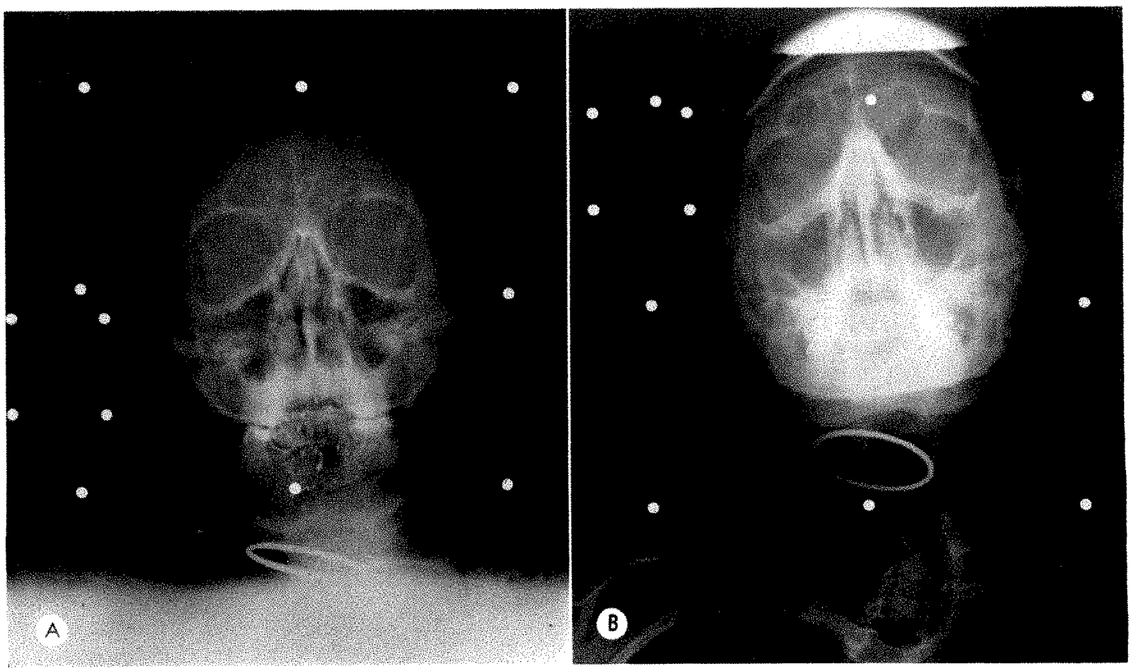


Fig. 6. (*A* and *B*) Stereo-roentgenograms of an interstitial seed implant of the undersurface of the tongue and floor of the mouth. The implant is composed of 17 gold 198 seeds with an activity of 0.925 mc radon-equivalent each at the time of implantation. The white dots indicate the images of the "fiducial points."

computed in a sagittal plane passing through the center of the implant (Fig. 7).

The present version of RADCOMP requires that for both types of roentgenograms, orthogonal and stereographic, the two images of a source must be matched manually before the input data are coded. However, at least three other programs[2,4,6] allow input data from orthogonal roentgenograms to be listed in random order with automatic matching of the two images of a source; this feature greatly reduces the time required to prepare input data and increases the accuracy of localization of sources. This capability is being incorporated into RADCOMP for both orthogonal and stereo-roentgenographic input data but is not yet operational on a routine basis.

THE CONVERSION OF DOSE IN ROENTGENS (PATERSON-PARKER) TO RADS

There have been more than three decades of successful clinical experience using the Paterson-Parker system[10] for assessment of dosage from individual implantations. With

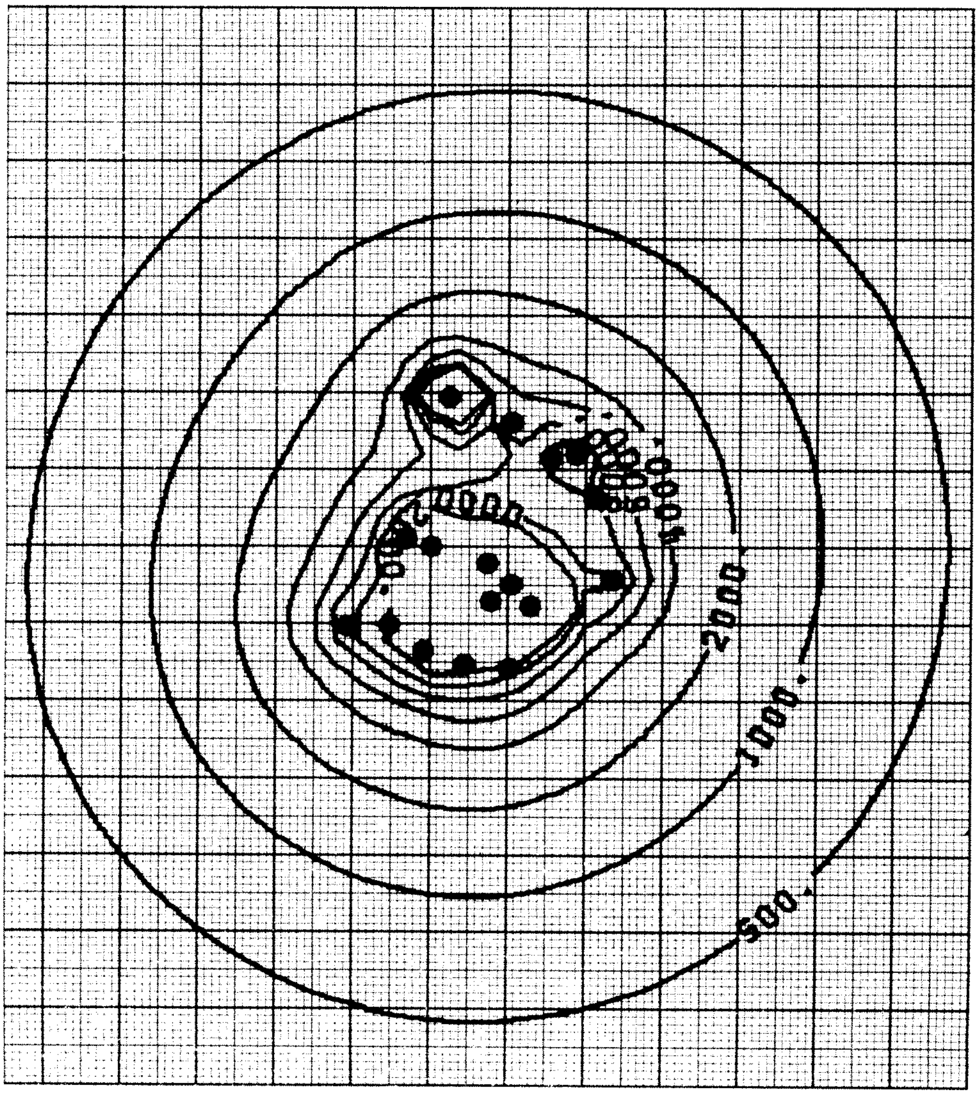


Fig. 7. Isodose curves around the seeds shown in Figure 6. A 1 mm. grid is in the background. The units are in rads.

the opportunity of developing full isodose distributions with electronic computers, it is important to ensure continuity of clinical experience between the Paterson-Parker system and the computer methods. Isodose curves are computed in rads while the Paterson-Parker tables were computed in roentgens with approximations included. To compare the results of the two methods quantitatively for interstitial implants, 4 factors must be considered:

SPECIFIC GAMMA-RAY EMISSION (Γ FACTOR)

The Paterson-Parker tables were prepared using 8.4 roentgens per hour as the dose rate in air from a point source of radium filtered by 0.5 mm. platinum. More recent measurements indicate that this dose rate is 8.25 roentgens per hour,[5] which is the value recommended by the International Commission on Radiological Units and Measurements.[8] Thus the dose rates derived from Paterson-Parker tables should be reduced by the ratio of 8.25/8.40.

OBLIQUE FILTRATION

In the preparation of the Paterson-Parker tables the attenuation of dose due to oblique filtration was not allowed for completely.[11,12] For this reason, the dose from a typical implant is approximately 2 to 4 per cent less than that calculated by the Paterson-Parker tables.

ATTENUATION OF GAMMA RAYS IN TISSUE

Since the Paterson-Parker tables give exposure dose in air, no allowance was made for the attenuation of gamma rays in tissue, which is about 1 per cent per 1 cm. for the gamma rays of radium up to a distance of 4 cm. as discussed previously.[15]

ABSORBED DOSE

For radium, the exposure dose in roentgens is multiplied by 0.957[7] to obtain the absorbed dose in muscle expressed in rads.

When all of the above correction factors are considered, the factor to convert Paterson-Parker dose in roentgens to rads in muscle varies from 0.897 to 0.910 for the planar and volume implants shown in Table 1. It is recommended that a si conversion factor of 0.90 rads per "ro gen" (as calculated from Paterson-Pa tables) be applied to obtain the abso dose in rads for volume implants planar implants at distances less than cm. At 2.5 cm. and beyond, the correc factor will be less due to increased atte tion in tissue.

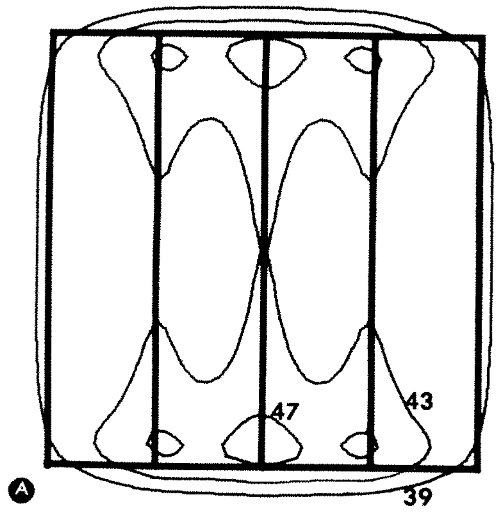
To confirm the validity of the ab conclusions, the relationship betw Paterson-Parker roentgens and rads been studied in another way: by analy several planar and volume implants ideal geometry and distribution. For e implant, 5 sets of isodose curves were tained which were equivalent to the Pa son-Parker stated dose multiplied by 0 0.88, 0.90, 0.92, and 0.94, as well as the rates 10 per cent above and 10 per cent

TABLE I

CORRECTION FACTORS TO CONVERT PATERSON-PARKER ROENTGENS TO RADS

(1) Γ Factor Correction: 8.25/8.40
(2) Absorbed Dose: 0.957 rads/roentgen

	(3) Oblique Filtration	(4) Tissue Absorption	Rad/Pate Parke Roentg (1)×(: ×(3)×(
Plane, 3×3 cm.,			
at 0.5 cm.	0.975	0.992	0.909
1.0 cm.	0.985	0.984	0.911
1.5 cm.	0.990	0.974	0.906
Plane, 4×4 cm.,			
at 0.5 cm.	0.972	0.991	0.905
1.0 cm.	0.982	0.981	0.905
1.5 cm.	0.987	0.972	0.902
Plane, 4.5×5 cm.,			
at 0.5 cm.	0.967	0.988	0.898
1.0 cm.	0.979	0.979	0.901
1.5 cm.	0.985	0.970	0.898
Volume, 3×3×3 cm.	0.975	0.986	0.904
Volume, 4×4×4 cm.	0.972	0.984	0.899



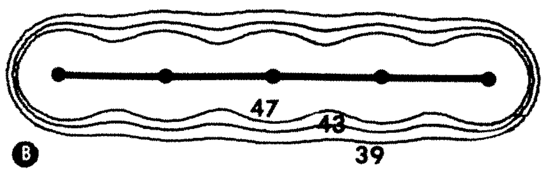


FIG. 8. Isodose patterns in the perpendicular midplane (A) and in a plane 0.5 cm. from a 4×4 cm. plane (B). All needles are radium, 0.66 mg./cm., 0.5 mm. platinum filtration. The isodose curves for the stated dose (Paterson-Parker roentgens) ×0.90 and the doses 10 per cent above and 10 per cent below this dose are shown. The units are rads per hour.

low each corrected Paterson-Parker dose. Isodose curves for 2 of the implants considered are reproduced here: a 4×4 cm. plane in Figure 8, A and B, and a 3×3×3 cm. cylinder in Figure 9, A and B. For the planar implants each correction factor was evaluated by considering the dose distributions in a plane 0.5 cm. from and parallel to the needles; in the area bounded by the projection of the peripheral needles the areas were measured which received equal to or greater than the 3 dose levels: the stated dose (the corrected Paterson-Parker dose), 10 per cent above, and 10 per cent below the stated dose. For example, the Paterson-Parker dose rate for the 4×4 cm. plane is 47.6 roentgens per hour at 0.5 cm. Using a correction factor of 0.90, the stated dose rate is 42.8 rads per hour; the

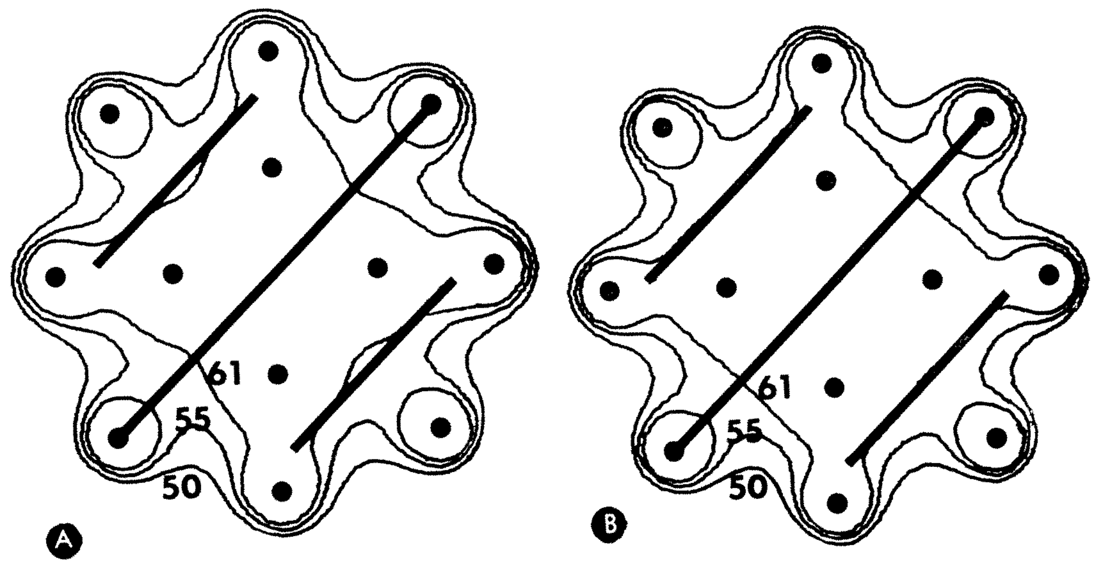


FIG. 9. Isodose patterns in the perpendicular midplane (A) and in the perpendicular plane 0.5 cm. inside the end (B) for a crossed cylindrical volume implant, 3 cm. in diameter and 3 cm. in length. All needles are radium, 0.33 mg./cm., 0.5 cm. platinum filtration. The isodose curves for the stated dose (Paterson-Parker roentgens) ×0.90 and the doses 10 per cent above and 10 per cent below this dose are shown. The units are rads per hour.

areas obtained for this plane were those bounded by the 42.8, 47.6, and 38.5 rads per hour isodose curves. The per cent of the areas for all planes using the 5 correction factors are shown in Table II. The data in Table II indicate that the choice of a correction factor represents a compromise between two situations: (1) delivering a dose which is not less than 10 per cent below the stated dose to all, or almost all, of the area; and (2) delivering a dose 10 per cent above the stated dose to as small an area as possible. From the clinical viewpoint the first consideration is certainly more important. From Table II, it is seen that the choice of a correction factor would likely vary between 0.89 and 0.91 for the implants considered. Thus, based on the criteria of the Paterson-Parker system, the factor 0.90, which was derived from other reasoning above, appears to be an acceptable conversion factor.

DISCUSSION

An important consideration is the clinical usefulness of the detailed information which the computer produces for individual implants. At this time, it is not possible to

Table II

ANALYSIS OF DOSE DISTRIBUTIONS AT 0.5 CM. FROM PATERSON-PARKER PLANAR IMPLANTS USING VARIOUS FACTORS TO OBTAIN DOSE IN RADS

Plane		Multiplicative Factors Used to Convert Paterson-Parker Roentgens to Rads in Muscle				
		0.86	0.88	0.90	0.92	0.94
3×3 cm. 2/3 periphery	(a)	99%	99%	98%	96%	93%
	(b)	88	73	66	61	57
	(c)	54	48	38	21	7
4×4 cm. 2/3 periphery	(a)	100	100	99	99	95
	(b)	72	55	37	27	21
	(c)	18	13	4	1	0
5×5 cm. 2/3 periphery	(a)	100	100	94	84	64
	(b)	52	41	29	21	16
	(c)	15	11	8	2	0
5×5 cm. 1/2 periphery	(a)	99	98	97	94	87
	(b)	82	78	74	71	69
	(c)	68	64	40	23	14
6×6 cm. 1/2 periphery	(a)	100	100	99	98	97
	(b)	89	79	77	73	59
	(c)	54	36	18	7	2
7×7 cm. 1/2 periphery	(a)	100	100	99	99	99
	(b)	99	87	73	52	32
	(c)	29	15	11	6	2

(a) Per cent of area receiving a dose greater than the level defined by 10 per cent below the stated dose.*
(b) Per cent of area receiving a dose greater than the level defined by the stated dose.*
(c) Per cent of area receiving a dose greater than the level defined by 10 per cent above the stated dose.*
* The stated dose is that dose derived from the Paterson-Parker tables multiplied by the indicated correction factor.

Note:
(1) All implants had radium distributed according to the Paterson-Parker rule: for planes of less than 25 cm.^{2}, two-thirds of the total radium is in the periphery of the area, and for planes between 25 and 100 cm.^{2}, one-half of the total radium is in the periphery of the area. Dose distributions for the 5×5 cm. plane were computed for both types of distribution.
(2) All implants were crossed at the active ends, as recommended in the Paterson-Parker system.

say whether cure rates can be improved with the availability of computer dosimetry. However, in a retrospective study, implants of previously treated tumors of the oral cavity were recalculated by computer.[3] Of the cases which were chosen because of local recurrence or necrosis, more than two-thirds of the complications could be explained on the basis of local underdose or overdose as revealed by the complete isodose distributions. Thus, it seems likely that the additional dosimetric information supplied by the computer calculations will be effective in upgrading the quality of treatment.

SUMMARY

A digital computer program has been developed to calculate dose distributions around interstitial and intracavitary radiation sources and the method has been in routine use for more than 3 years at The University of Texas M. D. Anderson Hospital and Tumor Institute at Houston. The features of the program and its clinical application are considered, in addition to the relationship between computer dosimetry and the Paterson-Parker system.

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EXPERIENCE WITH COMPUTERIZED IMPLANT DOSIMETRY*

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INTERSTITIAL implants with small encapsulated sources, inserted in the vicinity of a tumor and left permanently in the tissue, have been used extensively at Memorial Hospital since 1914. Up to 1955 interstitial implantations were carried out with radon 222 seeds,[1] which were pioneered at Memorial Center. Since 1956 refined implantation techniques (afterloading) and artificial isotopes, iridium 192, gold 198, and iodine 125 have been employed in addition to radon seeds.

About 150 to 200 patients a year are treated with internal radioactive sources. The majority of these cases received dosimetric analysis by the Department of Medical Physics. Until the advent of computerized methods, the dosimetry of internal radioactive sources depended upon source distribution systems which assign a single dose to the implant. Of these systems the Paterson-Parker and Quimby systems are the most widely used. However, the objectives of implant dosimetry are best served by a complete spatial description of the radiation dose produced by the implanted sources. Three-dimensional isodose distributions are essential to make treatment planning for internal radioactive sources comparable to external radiation beam therapy. A knowledge of the spatial distribution within an implant allows a better analysis and facilitates the choice of the addition of external fields. Our staff has been concerned with such aids as computerized systems for the calculation of the dose distributions of both external fields and implanted sources since 1955.[3,4] Our present computerized implant dosimetry system produces a dose matrix from which isodoses are drawn manually in any plane at any angle in relation to the implant. The three-dimensional dose matrix may be built up from the planar elements.

Since the computations are only as accurate as the available input information, several subroutines have been written to aid in the three-dimensional localization of implanted sources.[1] Figure 1, *A* and *B* shows a typical radon 222 seed implant. Figure 2, *A* and *B* shows the dose matrix in a plane as it is printed out by the computer, and the isodose information as it is generally entered into the patient's chart.

Figures 3, *A* and *B*, and 4, *A* and *B* demonstrate the input/output for a radium application for carcinoma of the cervix. While our computer program has the capability of printing out the dose matrix in any desired orientation it is generally sufficient to give anteroposterior and lateral dose planes through the source configuration.

In the majority of seed implants the sources are distributed uniformly throughout the implanted volume and do not follow a Paterson-Parker distribution, so the Paterson-Parker tables can not be used for these cases. A series of 25 consecutive radon seed volume implants, in which the sources were spaced uniformly, was analyzed with our computer system and reported in 1964.[2] The analysis disclosed that the average dose delivered by an implant is approximately represented by the Paterson-Parker dose. The minimum dose actually found in the implant, however, was approximately half that given

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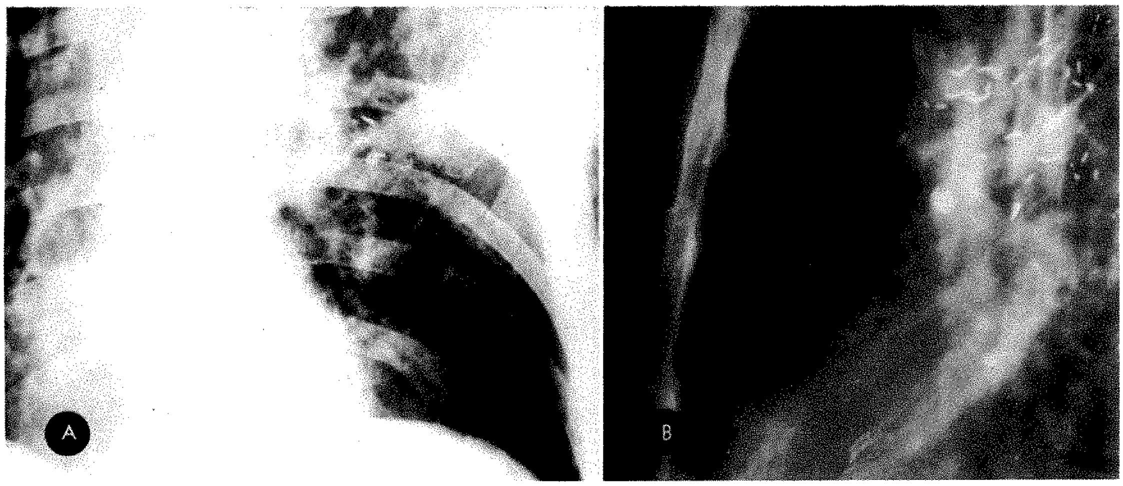

FIG. 1. Radon 222 seed implant No. 1. (*A*) Anteroposterior and (*B*) lateral localization.

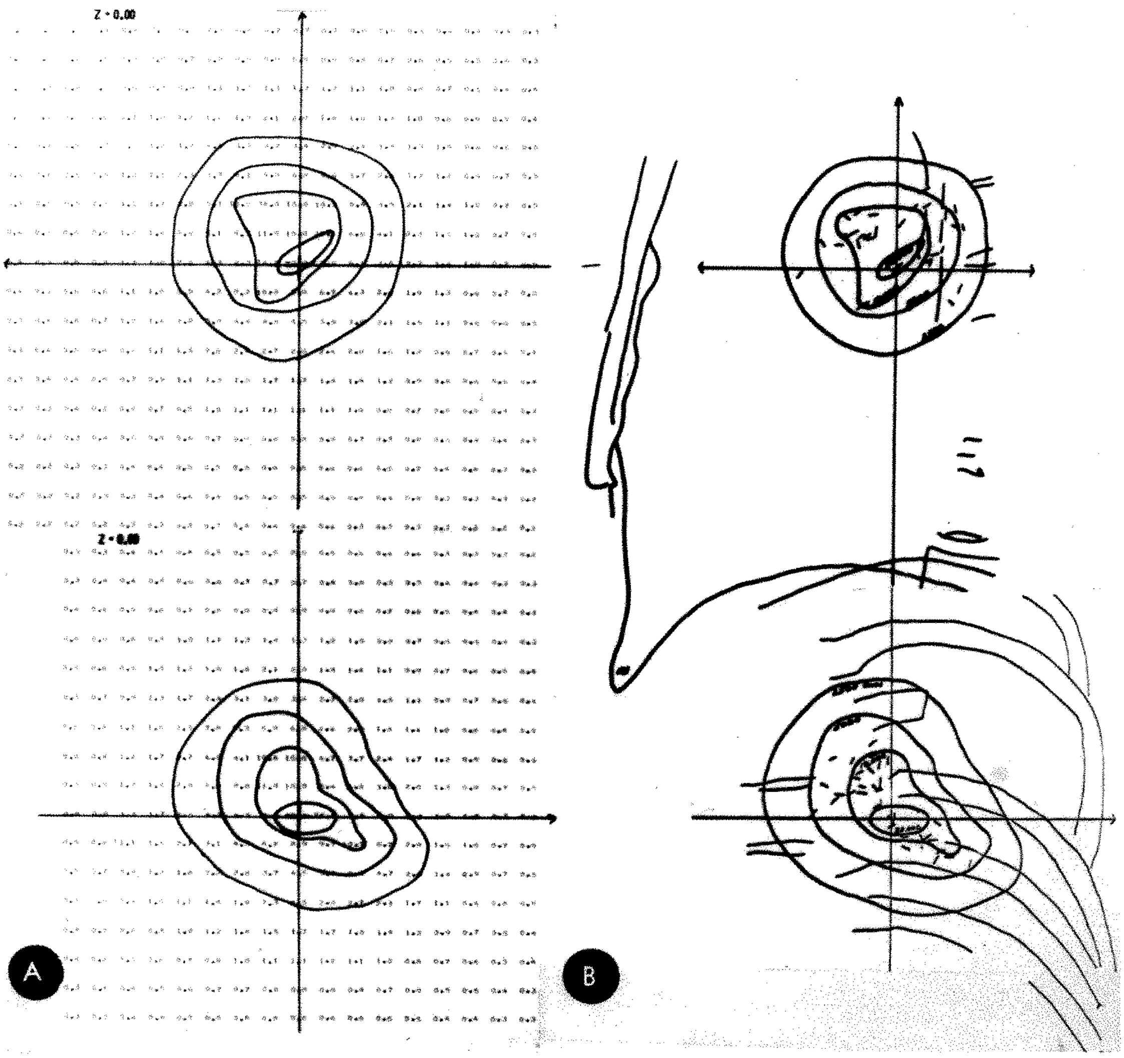

FIG. 2. Radon 222 seed implant No. 2. Computed dose matrix in (*A*) anteroposterior and (*B*) lateral planes passing through the center of the implant.

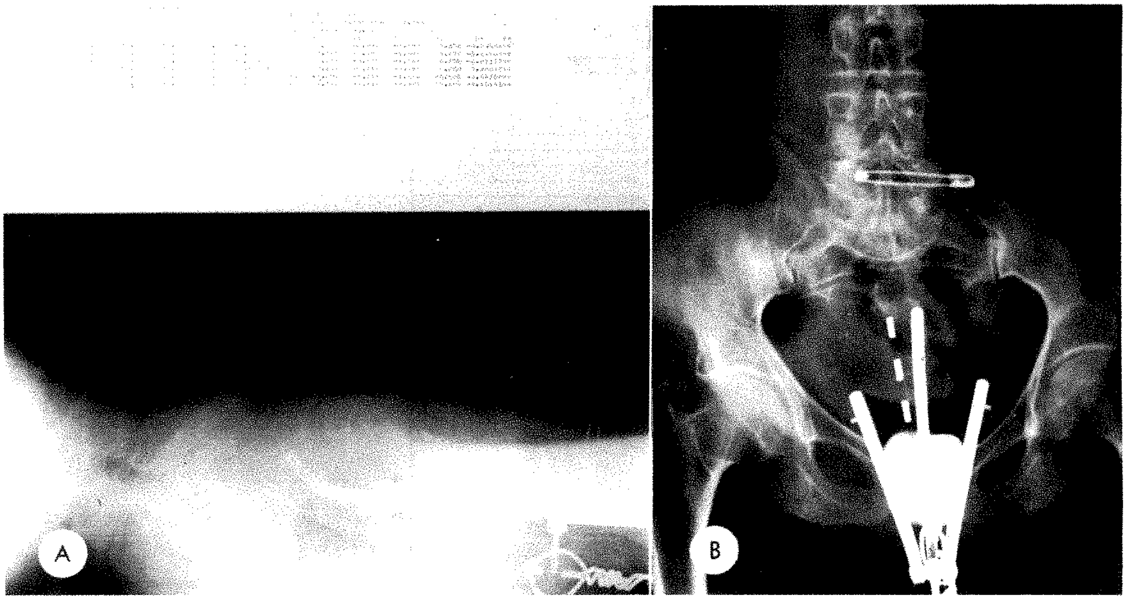

FIG. 3. Typical carcinoma of cervix radium 226 application No. 1. (*A*) Lateral and (*B*) anteroposterior roentgenographic projections.

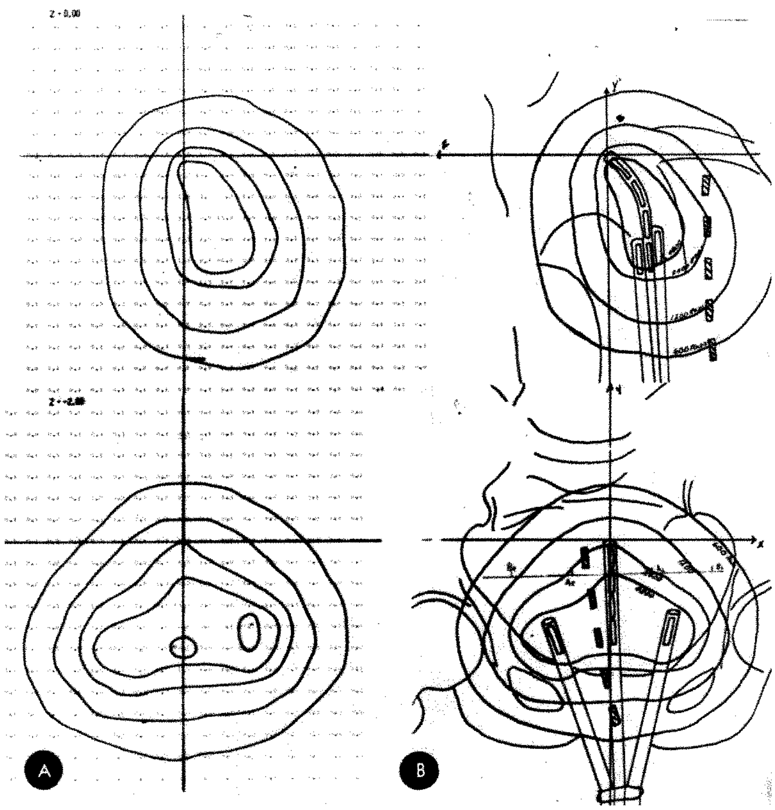

FIG. 4. (*A* and *B*) Carcinoma of cervix radium 226 application No. 2. Computed dose matrix in lateral and anteroposterior planes passing through the center of the lesion.

by the Paterson-Parker tables. It generally occurred on the periphery of a seed implant. One wonders whether the peripheral location of the minimum dose in these implants has been a contributing factor to their therapeutic success, in spite of the large differences between the average dose and the minimum dose.

Since December 1965, in an attempt to diminish the radiation exposure of personnel, low energy radioactive seeds have been developed at Memorial Hospital. Iodine 125 has a half-life of 60 days and a mean gamma energy of about 30 kev. (Table I). It was first used in 1960 for tracer studies in place of iodine 131 by Myers and Vanderleeden.[5] Xenon 133 and cesium 131, with half-lives comparable to that of radon 222, are more difficult to produce and their cost, therefore, is relatively higher.

There may be an advantage in the use of seeds such as iodine 125 with longer half-life than that of radon 222. Clinical experiences with 361 implants of iridium 192 performed at Memorial Hospital from 1956 to 1962, suggested that the continuous low dose rate over a long period of time had some therapeutic advantage. The local lesion in most cases was unresectable and often unfavorable for external radiation therapy; yet 22 patients have survived for 5 years or more.

Before iodine 125 seeds were approved for clinical use, the dose distributions obtainable with such seeds were investigated. Relative depth-dose curves were measured with lithium fluoride rod dosimeters, which were embedded in a mix-D phantom around an iodine 125 source. The depth-dose curves were normalized to rads by using an absorbed dose factor of 1.7 rads/mc-hr. at 1 cm. from an isotropic iodine 125 source. Three-dimensional dose distributions obtained with iodine 125 implants were computed on an IBM 1800 computer, and dose distributions were computed for radon 222 and iodine 125 sources arranged in identical configurations.

Figures 5, *A* and *B*, 6, *A* and *B* show two comparative sets of isodose curves as computed for radon 222 and iodine 125 in the same geometric arrangement. The activities were normalized to yield an equal dose per 1 mc destroyed at 1 cm. An analysis of the isodose curves indicates that the general distribution of the radiation within the implanted volume is nearly the same for iodine 125 as it is for radon 222. Beyond the periphery of the tumor, however, the radiation drops off much faster within an iodine 125 implant. The high spots within the 8,000 rad level contour indicate that the spacing for iodine 125 seeds ideally should be somewhat closer than for radon 222 seeds and should probably not exceed 1 cm.

Physically 1 mc destroyed of iodine 125 is equivalent to 3.4 mc destroyed for radon 222. This factor does not take into account any biologic difference due to the difference in half-lives. On the basis of clinical experience the activity per seed in a volume implant should be between 0.6 to 0.7 mc iodine 125.

A total of 72 interstitial implants with iodine 125 seeds were performed between December, 1965 and May, 1967. Most of the implanted lesions were previously treated by surgical excision or external irradiation. These interstitial implants may be subdivided into the following groups: Intraoral-15; intrathoracic-6; intra-abdominal-9; and superficial-45.

Evaluation of the effects of interstitial implants with iodine 125 indicates a close similarity with those of the high energy gamma-ray emitting isotopes radon 222

Table I

PHYSICAL CHARACTERISTICS OF LOW ENERGY GAMMA-RAY EMITTING ISOTOPES

Low Energy Seeds

	Half Life	Gamma Energy
Xenon 133	5.3 days	31–81 kev.
Cesium 131	9.7 days	29.4 kev.
Iodine 125	60.0 days	27.4 kev.

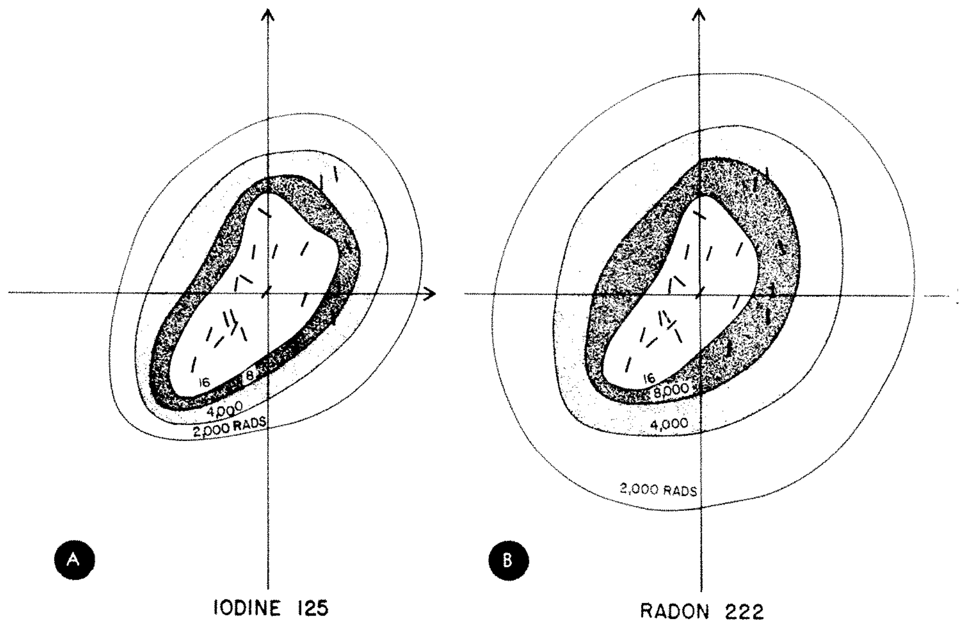

FIG. 5. (*A*) Typical isodose distribution obtained with iodine 125 seeds. (*B*) Isodoses were computed also for radon 222 seeds assumed to be in identical geometric arrangement. Anteroposterior projection. Normalization: equal dose at 1 cm. per 1 mc destroyed. Implanted area: right neck, 20 seeds.

and iridium 192. But the radiation exposure to personnel connected with interstitial implants has been decreased by a factor of 100 whenever iodine 125 seeds have been used. The exposure to those who come in contact with the patient after his discharge from the hospital is virtually eliminated.

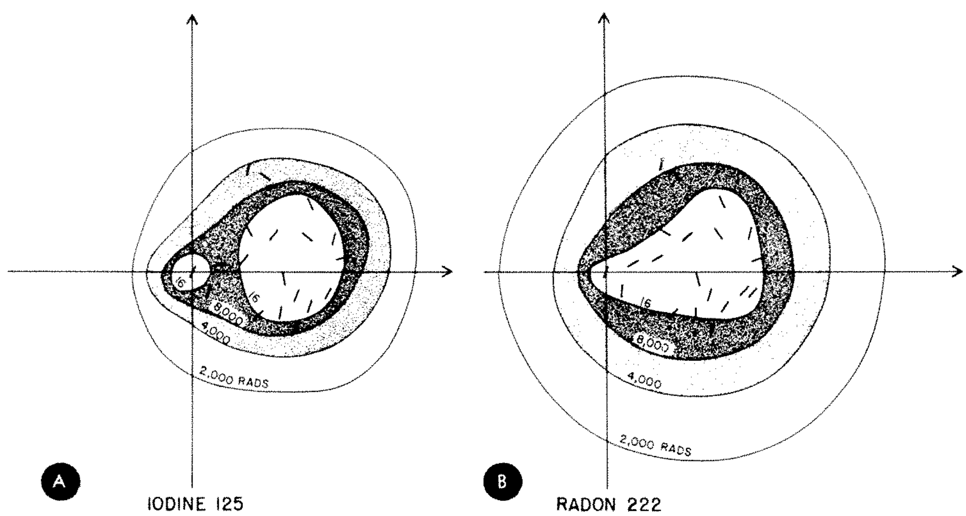

FIG. 6. (*A*) Isodoses are shown for an iodine 125 implant and (*B*) computation for radon 222 seeds assumed to be in identical geometric arrangement as in FIG. 5, *A* and *B*. Lateral projection. Normalization: equal dose at 1 cm. per 1 mc destroyed. Implanted area: right neck, 20 seeds.

SUMMARY

Computers, by their ability to perform many calculations accurately and rapidly, make it possible to obtain and display information which would otherwise not be feasibly obtainable. Computerized treatment planning for internal radioactive sources, as well as for external radiation beams, obviously provides a more accurate and more complete determination of radiation dosage; it also demands more precise clinical data and thus tends to raise the level of all the work in the radiotherapy center.

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DEPTH DOSE MEASUREMENTS WITH LITHIUM FLUORIDE*

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REFERENCE occasionally is made to lithium fluoride (LiF) dose measurements at depths within phantoms, animals or patients.[2,5,8] However, comparative LiF and ionization chamber depth dose measurements have not been reported. The lack of correlative depth dose measurements in degraded photon beams is surprising, since increased thermoluminescent response at low photon energies[1,6] may result in dose measurements with LiF which are higher than those measured with ionization chambers. Ionization chamber and LiF measurements of depth dose may be compared by measuring per cent depth dose curves by both methods. If identical depth dose curves are obtained, then LiF depth dose measurements are as acceptable as depth doses measured by more traditional ionization chamber techniques. Furthermore, LiF thermoluminescence dosimetry may provide a convenient method for measurement of per cent depth dose. The purpose of this paper is to compare the results of per cent depth dose measurements with LiF and ionization chambers.

METHOD

Harshaw TLD-100 LiF, annealed by the standard annealing procedure,[1] was sealed within polyethylene capsules and exposed at selected depths within a water phantom. Phosphor was stored for 24 hours before readout. Exposures to cobalt 60 radiation were made with a Picker C-10,000 teletherapy unit. X rays were supplied by a 250 kvp. General Electric Maxitron x-ray generator. Doses received varied between 5 and 100 rads, a range within which LiF luminescence is proportional to dose.[1,7] Luminescence was measured digitally with a Madison SL-2 thermoluminescence reader. Photomultiplier high voltage was selected to provide maximum ratios of (luminescence sample plus background)^2/(luminescence background).[6] Temperature of the heating pan reached 260°C. during the 40 second heating cycle. Per cent depth dose was calculated as 100 times the ratio of luminescence from LiF exposed at each selected depth to that from phosphor positioned at a depth of maximum dose (5 mm. for cobalt 60, surface for x rays). Ionization chamber per cent depth doses were measured with a 4 mm. internal diameter by 12.5 mm. long chamber designed to specifications described by Fedoruk, Johns and Watson.[3]

RESULTS AND DISCUSSION

Per cent depth dose measurements with LiF in water phantoms exposed to cobalt 60 radiation agree well (± 1 per cent) with ionization chamber measurements. Ionization chamber and LiF per cent depth dose data are compared in Figure 1 for a 10×10 cm. cobalt 60 field at 80 cm. source-skin distance. To prevent perturbation of central axis per cent depth dose, only 1 LiF capsule was present in the phantom during each exposure. Standard deviations of LiF per cent depth doses ($\sim \pm 1$ per cent) are shown. The solid curve in Figure 1 represents ionization chamber measurements

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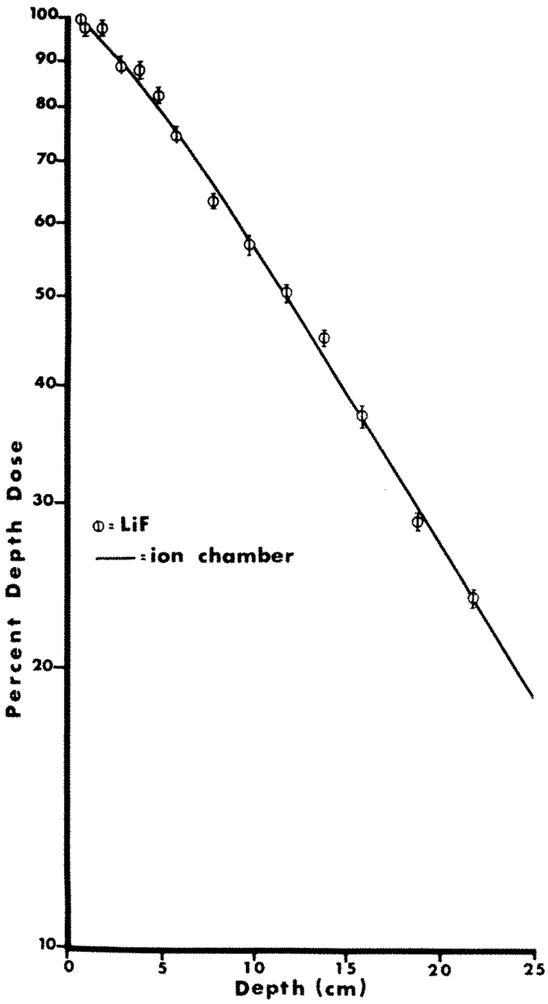

Fig. 1. Per cent depth dose, cobalt 60, 80 cm. source-skin distance, 10×10 cm. field, measured with LiF and ionization chamber.

of per cent depth dose for a 10×10 cm. cobalt 60 field at 80 cm. source-skin distance.

Influences were investigated of capsules at shallower depths on central axis per cent depth dose measured with LiF. Results in Table I suggest that per cent depth doses are measurable by 1 exposure to LiF filled capsules aligned at selected intervals along the beam central axis.

Ionization chamber and LiF measurements of per cent depth dose are compared in Figures 2 and 3 for small (6×6 cm.) and large (15×15 cm.) cobalt 60 fields.

Table I

Influence on LiF per cent depth dose measurements of LiF filled capsules at shallower depths along the beam central axis

No. of Capsules in Front	Per Cent Depth Dose at 12 cm.*
0	47.9±1.4
2	48.6±1.4
4	48.8±0.9
6	48.8±0.8

* Cobalt 60, 10×10 cm. field, 80 cm. source-skin distance.

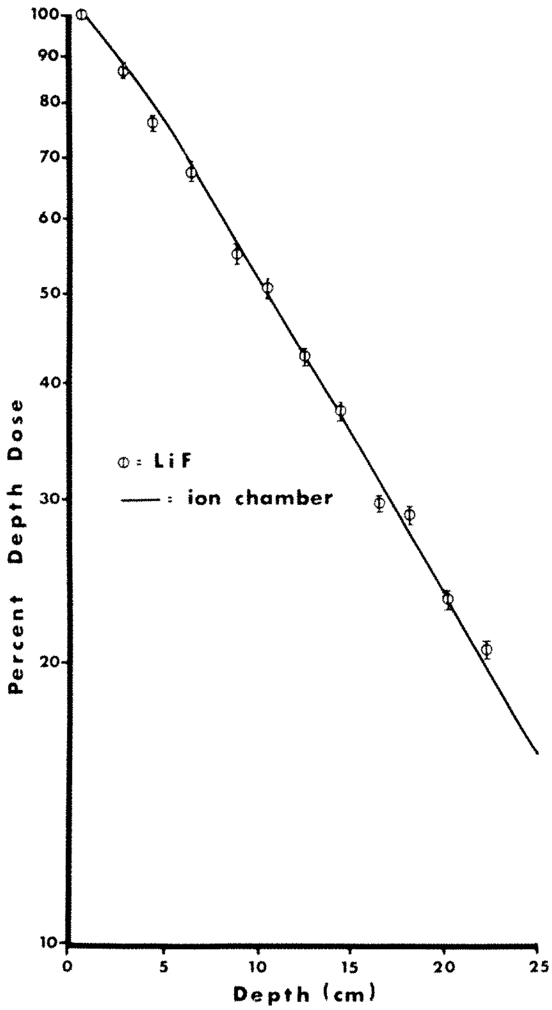

Fig. 2. Per cent depth dose, cobalt 60, 80 cm. source-skin distance, 6×6 cm. field, measured with LiF and ionization chamber.

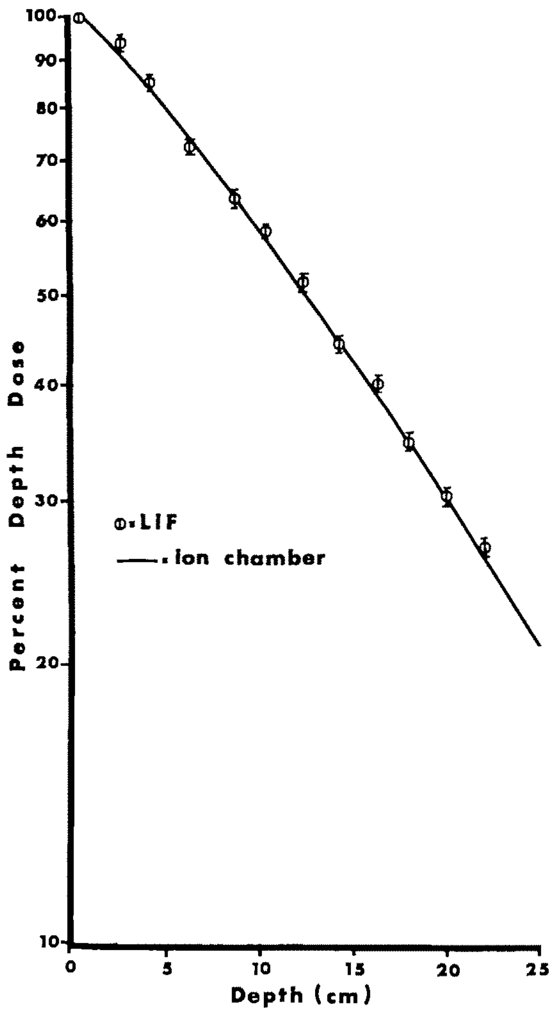

FIG. 3. Per cent depth dose, cobalt 60, 80 cm. source-skin distance, 15×15 cm. field, measured with LiF and ionization chamber.

Phosphor measurements were obtained by 1 exposure to capsules positioned at intervals along the beam central axis. Good agreement is apparent between LiF and ionization chamber measurements.

Unfortunately, per cent depth dose measurements with LiF exposed to orthovoltage x-ray beams were less successful.[4] Increased thermoluminescent response at low photon energies causes displacement of LiF per cent depth dose curves from those measured with ionization chambers. Problems encountered during measurement of surface doses also contribute to inaccuracies in LiF measurements of orthovoltage x ray per cent depth dose. Resolution of these difficulties is currently under study.

SUMMARY

Per cent depth doses were measured with LiF in water phantoms exposed to orthovoltage x rays and cobalt 60 radiation. Agreement within ±1 per cent was achieved between LiF and ionization chamber measurements of cobalt 60 per cent depth dose. Unsatisfactory results were obtained with LiF measurements of per cent depth dose from orthovoltage x rays.

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SAFE ENCAPSULATION PERIOD FOR SEALED MEDICAL RADIUM SOURCES*

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THE possibility of pressure accumulation within a sealed capsule containing radium was recognized by Madame Curie, who recommended that the glass encapsulated radium standards she prepared be opened at regular 15 year intervals to relieve the internal pressure.[3] The possibility of internal pressure arises from three causes: radon daughter products, helium from emitted alpha particles, and hydrogen and oxygen gas from water decomposed by alpha bombardment.[4] The accumulation of gas pressure in sealed radium containers has been calculated for sources of the type used medically.[10] From these calculations, it was concluded that medical sources of radium enclosed in platinum-iridium cylinders would accumulate a negligible pressure due to radon generation; about one atmosphere of pressure per year per milligram due to helium; and very much more than that from the decomposition of water into hydrogen and oxygen if the radium source contains water of hydration or is not otherwise dry. In that publication,[10] as well as in a later consideration of the problem,[6] it was recommended that medical radium sources be opened at least every 10 years in order to relieve the gas pressure.

It is the purpose of this report to consider the tolerable pressure build-up in radium tubes and needles by calculation and experiment, in order to generate data for re-evaluation of the period that a sealed radium source may be utilized before reopening becomes necessary. Only sources encapsulated in platinum-iridium alloy utilized for gamma-ray therapy will be considered; radium beta-ray applicators, such as plaques or nasopharyngeal applicators in monel metal, will not be considered.

If radium capsules are to be opened every 10 years, as has been suggested, radium then loses the major advantage it has over Cs^{137} as a radioactive source for temporary interstitial and intracavitary implants. Ra^{226}, with a half-life of 1,615 years, decays about 1 per cent every 23 years and thus seldom requires calculative depreciation of its radioactive content. Cs^{137}, with a half-life of 30 years, decays approximately 2 per cent per year and would need to be replaced every 5 to 10 years, according to the limits of treatment variation which a practitioner is willing to accept. Thus, the use of Cs^{137} has the disadvantages of source depreciation and frequent source replacement in radiation treatment; however, the advantage of radium is largely offset if radium capsules must be reprocessed every decade. Since it is common knowledge that many radium sources have been utilized for as long as 50 years without explosion, the question of the genuine hazard involved and the period for which radium sources can remain sealed is an important one.

A review of the radium incidents reported[1,2,5,11,15] reveals that in each instance of spontaneous rupture (to our knowledge) the radium container was made of glass, thin-walled monel metal, or of platinum-iridium alloy with pressure-fitted plugs. The latter type of construction was common in the early part of the century, but probably has not been used in more than 30 years.[8] In addition, it is possible that the tubes which underwent spontaneous rupture were loaded with radium bromide, which has water of hydration. At least one supplier (there may be others) of radium

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sources for the past 30 years has used only well-dried radium sulfate for loading.[8] One supplier also adds platinated asbestos as a catalyst to recombine the dissociated hydrogen and oxygen gases which may have formed. Modern medical sources are loaded as fully as possible with radium sulfate, together with barium sulfate as inert filler. These compounds do not have water of hydration and are not hygroscopic. In addition, the salts are heated to 700°C. prior to sealing and to 1,100°C. to 1,500°C. during sealing to ensure dryness. By these means the possibility of pressure accumulation due to decomposition of water is eliminated. Radium sulfate should be completely dehydrated by heating in dry air at 300°C.[18]

CALCULATION OF PRESSURE

There are 5 alpha particles emitted by the daughter products of radium 226 in reaching stable lead 206. The first 4 alpha particles are released for each radium disintegration after an equilibrium period of 1 month or so. The fifth alpha particle emitted by polonium 210 is preceded by lead 210, radium D, which has a half-life of 21 years. Thus, nearly 100 years would be required for the emission of the fifth alpha particle to come into equilibrium with the radium decay rate. An approximate but adequate formulation of the number of alpha particles accumulated in a sealed radium source per milligram is as follows:

$$n = k \int_0^T e^{-\lambda_a t}(5 - e^{-\lambda_b t})\,dt, \qquad (1)$$

$$n = 1.17 \times 10^{15}(11{,}600 + 29.8e^{-0.0330T} - 11{,}600e^{-0.000429T})\,\alpha/\text{mg.-year}, \qquad (2)$$

where n is the total number of alpha particles emitted per mg. radium in time T; t is time; λ_a is the disintegration constant of Ra^{226}, 0.000429 years^{-1}; λ_b is the disintegration constant of Pb^{210}, 0.0330 years^{-1}; T is time in years elapsed since sealing of the radium source; k is the number of disintegrations per mg.-year, 1.17×10^{15}. In this formulation, the half-life of polonium 210 ($T\frac{1}{2} = 138$ days) is neglected. This approximation results in a 2 per cent overestimation of n at the end of 10 years, and a lesser error at greater times.

The alpha particles acquire orbital electrons to become $_2He^4$, a monatomic gas. One mole of helium contains 6.02×10^{23} molecules and occupies 22.4×10^6 mm.^{3} volume at standard temperature and pressure (STP). One atom of helium gas thus occupies the volume, V_a,

$$V_a = \frac{22.4 \times 10^6 \text{mm.}^3}{6.02 \times 10^{23} \text{ atoms}} = 3.72 \times 10^{-17} \text{ mm.}^3/\text{atom}.$$

The volume occupied by helium gas at STP generated per mg. radium in time T is as follows:

$$\text{Volume} = n \times V_a = 4.35 \times 10^{-2}(11{,}600 + 29.8e^{-0.0334T} - 11{,}600e^{-0.000429T}) \text{ mm}^3./\text{mg}. \qquad (3)$$

The volume occupied at STP by the helium liberated by 1 milligram of radium at various times after encapsulation as calculated by Equation 3 is shown in Figure 1.

STRENGTH OF SOURCE CONTAINER TO INTERNAL PRESSURE

To determine the internal pressure at which a platinum-iridium needle or tube will rupture, liquid at measurable pressures was forced into the container until rupture occurred. Rupture always occurred by a tear parallel to the long axis of the cylindrical container, as shown in Figure 2. The containers were new, but in some instances were bent repeatedly to simulate bending that sometimes occurs in use. The bending was done before and during the application of pressure; however, bending did not influence the internal pressure that the container would withstand. Several types of containers were employed in these tests (Table 1). The observations labeled M.D.A. were by the authors; those labeled U.M.

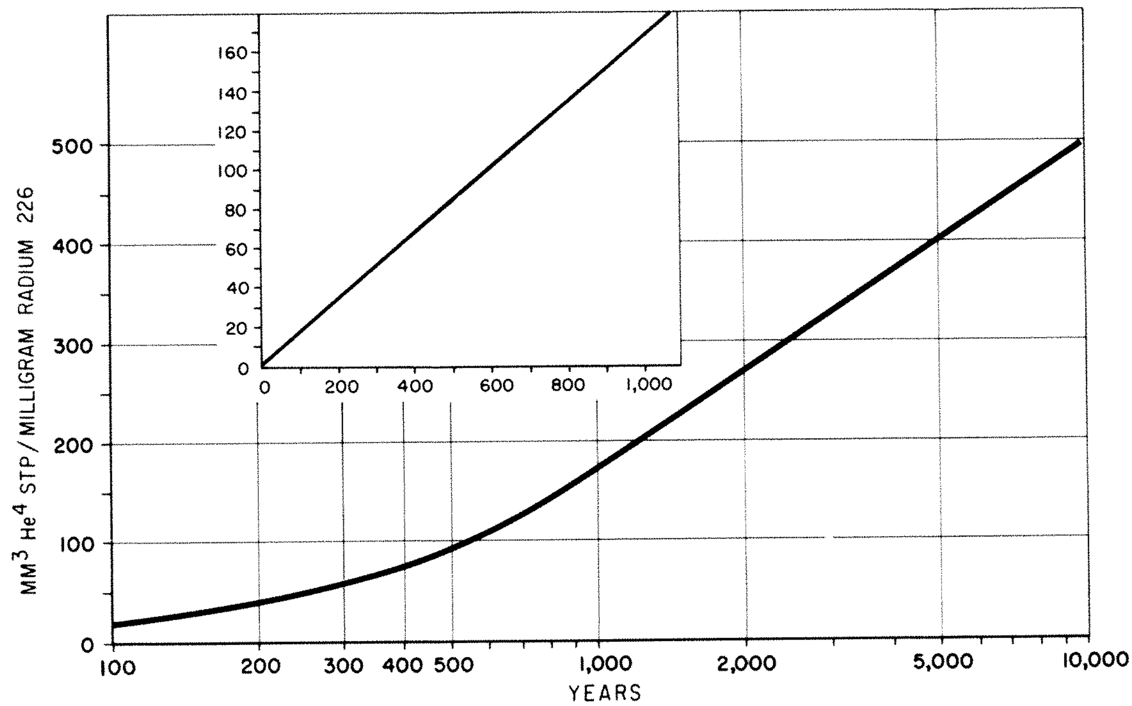

FIG. 1. Volume of helium gas in mm.^{3} at standard temperature and pressure (STP) formed per mg. of radium 226 plotted against years as determined from Equation 3.

were the result of independent experiments by George.[7]

Barlow's equation[14] is a method for the calculation of the strength of a cylindrical container with a thick wall:

$$S_t = \frac{pi[2 + 4t/di + 4(t/di)^2]}{4[t/di + (t/di)^2]}, \quad (4)$$

where S_t is the tensile strength expressed in PSI (pounds per square inch); t is the thickness; di is the internal diameter; pi is the internal pressure in PSI.

The handbook value of the ultimate tensile strength (S_t) of annealed 90 per cent platinum, 10 per cent iridium alloy is 55,000 PSI.[9] Using this value for S_t, the curve labeled "rupture" in Figure 3 was calculated from Barlow's equation (Equation 4 above). The experimental data from Table 1 are also plotted. The remarkable agreement between the experimental observations and the calculated curve gives confidence that calculations by Barlow's equation are correct and that the properties of the containers are not altered by the manufacturing processes. The curve labeled "safe" was calculated by Barlow's equation with $S_t = 11,000$ PSI, that is, with a safety factor of 5. It is this curve that is employed for the estimation of the safe encapsulation period for various sources that appear in this report.

SAFE ENCAPSULATION PERIOD

The pressure due to the accumulation of helium gas is dependent upon the free gas volume within the container. The manufacturers of radium sources have provided this information.[7,12] For doubly encapsulated sources, only the strength of the outer sheath is considered.

Utilizing the information developed in Figure 1 and 3, years of safe encapsulation are plotted against space per mg. of radium for various ratios of wall thickness to internal diameters (Fig. 4). Thus, from these curves, the time of safe encapsulation can be determined for any radium source made from 90 per cent platinum, 10 per cent

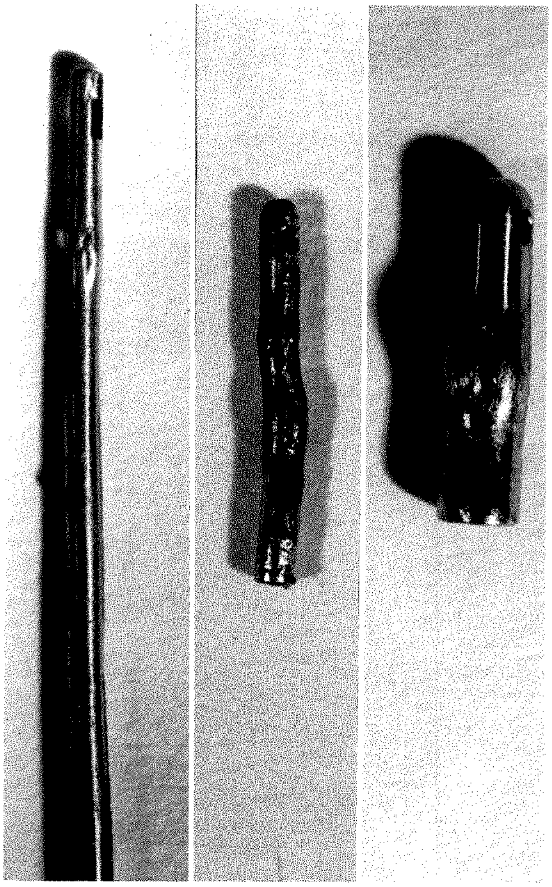

FIG. 2. Photographs of ruptured radium containers.

iridium alloy, provided the internal diameter, wall thickness, and free gas volume are known. In Table II, the safe encapsulation period, derived by the above method, is given for a number of different sources. It is seen that the safe encapsulation period ranges upward from 450 to over 10,000 years. The fact that the inner container adds to the strength of the whole encapsulation has not been considered and is an additional safety factor.

POSSIBILITY OF DIFFUSION OF HELIUM THROUGH THE CONTAINER

It is possible that the seal of a sealed source might be sufficiently good to prevent the leakage of radon but not adequate to prevent helium from passing through. To investigate this possibility of reduction

TABLE I

RUPTURE TESTS OF MEDICAL RADIUM CONTAINERS (90 PER CENT PLATINUM, 10 PER CENT IRIDIUM ALLOY)

Institution Conducting Test*	Active Length	Internal Diameter (*di*)	*t* (mm.)	*t/di*	Remarks	Experimental Rupture Pressure (PSI)
M.D.A.	12 mm.	0.75 mm.	0.5	0.67	New, undamaged	40,000
M.D.A.	12 mm.	0.75 mm.	0.5	0.67	Bent 5 times to 45°	45,000
M.D.A.	12 mm.	0.75 mm.	0.5	0.67	Test of seal	40,000
M.D.A.	45 mm.	0.85 mm.	0.4	0.47	New, undamaged	20,000
M.D.A.	45 mm.	0.85 mm.	0.4	0.47	Bent 6 times to 70°	20,000
M.D.A.	45 mm.	0.85 mm.	0.4	0.47	New, undamaged	20,000
M.D.A.	45 mm.	0.85 mm.	0.4	0.47	New, undamaged	20,000
M.D.A.	45 mm.	0.85 mm.	0.4	0.47	Bent to 45° at 8,000 PSI, bent to 45° at 10,000 PSI	20,000
M.D.A.	45 mm.	0.85 mm.	0.4	0.47	Bent, scratched, scored	32,000
M.D.A.	9 mm.	1.55 mm.	1.0	0.65	New, undamaged	60,000
M.D.A.	9 mm.	1.55 mm.	1.0	0.65	New, undamaged	60,000
U.M.	15 mm.	0.85 mm.	0.4	0.47	New	36,000
U.M.	12 mm.	0.70 mm.	0.5	0.71	New	>42,000
U.M.	16, 2 mm.	1.0 mm.	0.9	0.9	New	>45,000
U.M.	15 mm.	0.6 mm.	0.1	0.17	New	16,000

* M.D.A., Tests conducted at The University of Texas M.D. Anderson Hospital and Tumor Institute, Houston, Texas.
U.M., Tests conducted at Union Minière Du Haut-Katanga, Brussels, Belgium.

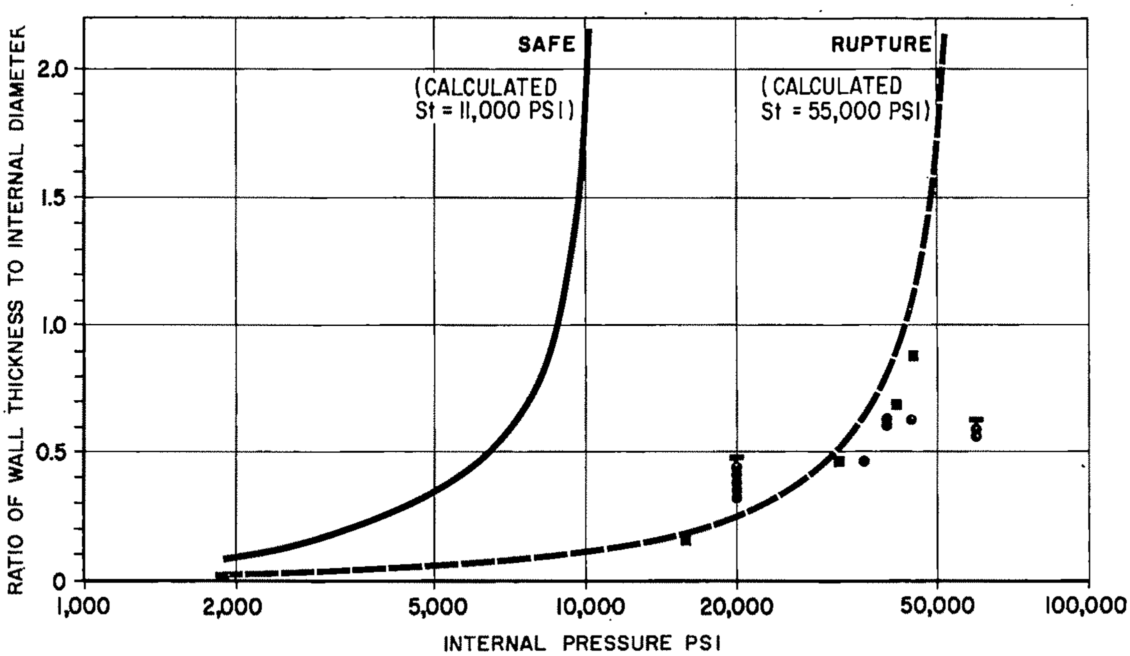

FIG. 3. Ratio of wall thickness to internal diameter, t/di for cylinders of 90 per cent platinum–10 per cent iridium alloy *vs.* internal pressure, PSI (pounds per square inch). The curves are calculated utilizing Equation 4, Barlow's equation, for thick cylinders. The curve labeled "rupture" utilized the Handbook value[9] of 55,000 PSI for the ultimate tensile strength, S_t, for annealed 90 per cent platinum–10 per cent iridium alloy. The plotted points are from the experimental rupture of radium tubes and needles of the same alloy by internal liquid pressure as detailed in Table I. The squares are from experiments by George[7] and the circles, by the authors. The rectangles indicate the point where all the circles immediately beneath should be plotted. The two sets of experiments were completely independent. The curve labeled "safe" was calculated using Equation 4 with $S_t = 11{,}000$ PSI; that is, with a safety factor of 5.

TABLE II

FREE GAS VOLUMES WITHIN SEALED MEDICAL RADIUM SOURCES AND CALCULATED SAFE ENCAPSULATION PERIOD

Description	Radium Content (mg.)*	Active Length (mm.)	Internal Diameter (mm.)	Wall Thickness (mm.)	t/di	Free Gas Volume (mm.³)			mm.³/mg.² Radium	Safe Encapsulation Period, Years, Safety Factor = 5
						Within Cell	Space Cell-Sheath	Total		
Needles, Direct Filling, Single Sheath	1 (U.S.A.)	11.0	0.6	0.5	0.833	0.54	—	0.54	0.54	2,500
	5 (U.S.A.)	7.0	0.7	0.5	0.715	1.04	—	1.04	2.208	550
	10 (U.S.A.)	12.0	0.7	0.5	0.715	1.69	—	1.69	0.169	450
Needles, Double Encapsulation	1 (U.M.)	15.0	0.85	0.4	0.471	1.88	1.15	3.03	3.03	>10,000
	1 (U.S.A.)	11.0	0.85	0.4	0.471	0.54	0.38	0.92	0.92	4,900
	1 (B1 R.C.C.)	15.0	0.60	0.60	1.00	2.32	1.53	3.85	3.85	>10,000
	1 (S4 R.C.C.)	15.0	0.60	0.50	0.83	2.32	1.53	3.85	3.85	>10,000
	2 (U.M.)	15.0	0.85	0.40	0.471	1.90	1.15	3.05	1.52	>10,000
	5 (U.S.A.)	7.0	0.95	0.40	0.421	1.04	0.73	1.77	0.354	800
	10 (U.S.A.)	12.0	0.95	0.40	0.421	1.69	1.08	2.77	0.277	580
Tubes, Double Encapsulation	10 (U.M.)	15.0	1.11	1.00	0.90	2.56	1.42	3.98	0.398	1,150
	10 (R.C.C. T6)	15.0	0.85	1.00	1.18	4.66	2.04	6.70	0.67	6,000
	10 (R.C.C. G2)	13.5	2.0	1.00	0.50	23.2	4.46	27.66	2.76	>10,000
	25 (U.S.A.)	10.0	3.55	1.75	0.514	8.03	1.83	9.86	0.39	1,030
	50 (U.S.A.)	13.0	4.05	2.25	0.40	20.44	3.10	23.54	0.47	1,100

* U.M., Union Minière Du Haut-Katanga, Brussels, Belgium.
R.C.C., Radio Chemical Centre, Amersham, England.
U.S.A., Made by Union Minière Du Haut-Katanga. Sold through Radium Chemical Co., New York.

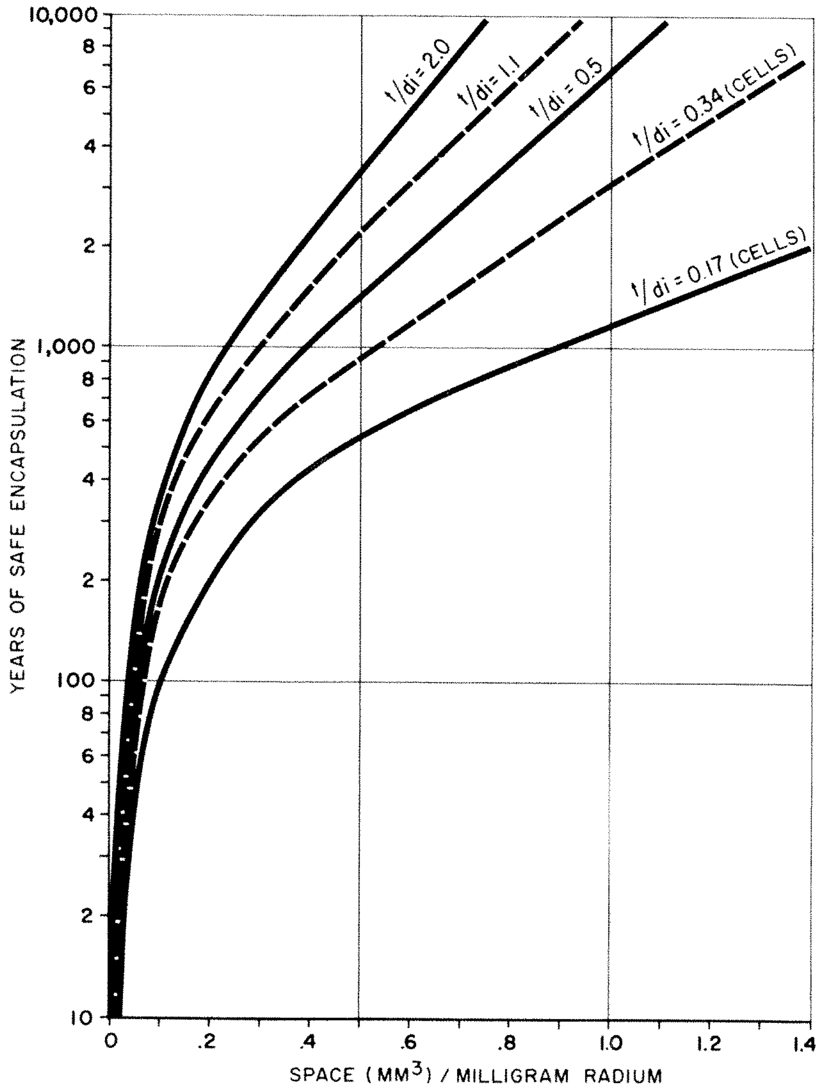

FIG. 4. Safe encapsulation period *vs.* gas space per mg. radium within cylinders of 90 per cent platinum–10 per cent iridium alloy. Curves are plotted for various ratios of wall thickness to internal diameter. A safety factor of 5 below rupture pressure has been allowed.

of helium pressure, two 3 mg. needles, which had been used for more than 20 years, were first leak tested for radon leakage using activated charcoal in a sealed container. A 7 day leak test indicated no detectable radon leakage.

The individual needles were then placed in a glass tube, evacuated to a pressure of 10^{-5} mm. Hg, and sealed. To increase the sensitivity of the test, the needles were left as long as 23 hours in the evacuated tube. The tube containing the source was placed within an outer tube which was sealed into the detection port of a mass spectrometer* which in turn was evacuated. At this time mechanical pressure was exerted on the surrounding tubing to break the inner glass tube, allowing accumulated helium to enter the spectrometer.

In each of three tests, a very small rate

* Consolidated Electrodynamics Corp. Model 24-120B.

of helium released outside of the source was detected ($2-3\times 10^{-8}$mm.^{3}/year). It is possible that what was taken to be helium could have resulted from surface contamination of the needle which was not detectable by the leak testing methods, since the helium detecting system was about 6,000 times more sensitive than the charcoal and Geiger-Müller tube method used for leakage tests. However, this amount of surface contamination is above the acceptable standard set by the manufacturer.[7] It was concluded that the leakage of helium through the container, though perhaps possible, does not serve to release helium gas pressure within a sealed platinum-iridium container.

MEASUREMENT OF ACCUMULATED PRESSURE WITHIN RADIUM SOURCES

An effort was made to observe experimentally the pressure within sealed radium sources. The device for these measurements, shown in Figure 5, provides a

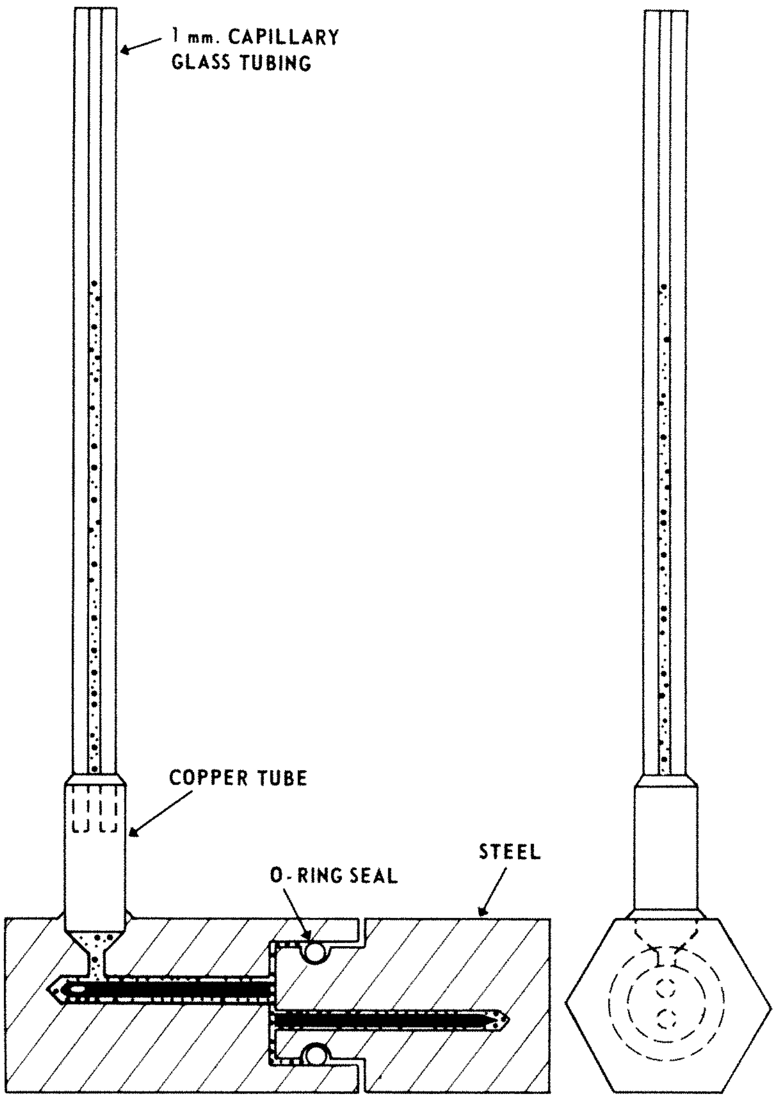

Fig. 5. Device used to shear radium container and measure pressure by change in water level in capillary.

method for shearing a radium source and measuring the release of gas. A change of ½ mm. in water level could be detected. Several sources were experimented upon in this way; one of certain pedigree was a 1.25 mg. source encapsulated 25 years earlier. For this source, a change of 4 mm. in water level would be expected from the calculation of helium gas volume. No change in level was observed for this or any of the sources. The experimental method employed can be criticized for its marginal sensitivity; however, it is fair to conclude that the true pressure developed within a radium source is not likely to be more than that calculated, and may well be less. Occlusion of the helium gas within the structure of the radium sulfate and barium sulfate crystals has been speculated upon.

CONCLUSION

Calculations of the strength of 90 per cent platinum, 10 per cent iridium alloy cylindrical radium source containers have been verified experimentally by the rupture of containers with internal pressure. Allowing a safety factor of 5, it is apparent that the danger of spontaneous rupture of such sources, from accumulation of internal gas pressure, is remote. There is evidence that pressure build-up is less than calculated, but even in the event pressure does build up at the calculated rate, sources encapsulated by modern methods are safe from spontaneous rupture for 400 or more years. It would appear that a good inspection program is better than an arbitrary time period for re-encapsulation. Surface scratches and severe wear, which reduce the wall thickness, should be a greater reason for replacement than the age of the container.

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EDITORIALS

NINTH INTER-AMERICAN CONGRESS OF RADIOLOGY

HAVING previously visited eight other American countries, the Ninth Inter-American Congress of Radiology brought us to Punta del Este, the renowned beach resort of Uruguay. If the scenic environment was indeed beautiful, the medical setting was also highly stimulating, for the little country has been and continues to be a source of important medical research and of fruitful original contributions; Uruguay has produced some of the most renown teachers of radiology in South America.

The Congress was well attended, as usual, with an important representation from the United States. The official U. S. Delegation was formed by: H. L. Abrams, M.D., Section on Radiology, American Medical Association; G. D. Davis, M.D., American Roentgen Ray Society; W. S. Maxfield, M.D., Society of Nuclear Medicine; J. E. Miller, M.D., American College of Radiology; F. H. Squire, M.D., American College of Radiology; W. T. Snow, M.D., American College of Radiology; and J. A. del Regato, M.D., Radiological Society of North America, American Radium Society, American Society of Therapeutic Radiologists, *Chairman*.

By sad coincidence, President Gestido of Uruguay died in the early hours of the very day in which he was expected to inaugurate the Inter-American Congress; the solemnity of the occasion was heightened by his absence. This unexpected event forced sudden changes in the social program of the Congress but the scientific sessions proceeded as scheduled. The excellent quality of the program, the scientific and technical exhibits were all a credit to Dr. Leandro Zubiaurre, President of the Congress and to his earnest associates who were on duty at any time to make sure that everything fitted the occasion. A special word of praise must be accorded to Dr. Helmut Kasdorf, Secretary, and his wife, Dr. Olga Barcia de Kasdorf, whose sustained and untiring efforts and patience, before and during the Congress, were the most important single cause of its success.

Among the features of the program were an important symposium on mammography, a session on congenital bone distrophies and another on nuclear scanning. A truly international symposium on time-dose relationships in radiotherapy brought together experts from England, Finland, France, North and South America.

The social program provided an unusual opportunity to appreciate the artistic and folkloric charms of the nation and offered an occasion to renew affectionate ties, between persons and families, and to marvel at the prodigal, yet unassuming hospitality of our neighbors. The members present of the International Club of Radiotherapists had an informal interchange of views as guests of Dr. and Mrs. H. Kasdorf at their chalet in Punta Ballena.

As in previous Congresses, a ceremonial convocation of the *American College of Radiology* was staged, to honor Latin American radiologists. Dr. Fay H. Squire officiated as President of the College, Dr. J. E. Miller as Chairman of the Board of Chancellors, Dr. J. A. del Regato as Secretary and Dr. W. T. Snow as Sergeant-at-Arms. The cap and gown procession, formed by American Fellows and by Latin American Honorary Fellows of the College, brought to the stage three candidates to be honored: Dr. Leandro Zubiaurre, Professor

of Radiology of the University of Uruguay; Dr. Raúl Leborgne, for his long and fruitful work in mammography; and Dr. Manuel O. Zariquiey, International Coordinator for the Eastman Kodak Company's Radiography Markets Division, for his devotion to Inter-American activities in Radiology and for the sustained cooperation he has offered to the College in these tasks.

The parent institution of these Congresses, the Council of the *Inter-American College of Radiology*, met before and during the Congress; it is formed by one representative from each of the countries of the New World. The Council made important changes in the Statutes and moved to offer the necessary support to Dr. Guillermo Pezet in his untiring efforts as editor of *Revista Interamericana de Radiología*, official organ of the College. The Council also decided to hold the Tenth Congress in San Juan, Puerto Rico, in 1971.

The Centre Antoine Béclère, of Paris, through its special emissary Prof. E. Cherigié, conferred its Gold Medal on Dr. Oscar Soto, of Lima, departing President of the Inter-American College and outstanding radiologist of Latin America.

The swiftness of modern travel over high mountains, across vast jungles and along sierras and rivers, does convey an artificial sense of proximity. Equally vast socio-economic differences and problems and diverse cultural influences keep us from truly identifying this proximity. Sporadic contact and snappy judgments contribute to give us a caricature of each other and a stereotype of our concerns, for the most part detached and fictional, and not conducive to friendly relationships; polite and respectful segregation yield asperities and arrogance. Health is the prelude of all cultural influences and medical interchange is among the most generous and truly universal beneficent forces. True to this tradition the Inter-American Congresses of Radiology have become a very needed opportunity for contact among radiologists of the Americas.

J. A. del Regato, M.D.
Chairman, U.S. Delegation

Penrose Cancer Hospital
2215 North Cascade Avenue
Colorado Springs, Colorado 80907

FRANÇOIS BACLESSE, M.D.
1896-1967

DR. BACLESSE died after a sudden illness on November 11, 1967. All those who have met him knew his almost exclusive passion for his work and it was during a consultation that he was suddenly attacked by the disease that took him away.

A native of Luxembourg, but with remote French forefathers, he carried out nearly all his medical practice in France, in Paris.

The Fondation Curie had been for years his home, his life. In 1926, he began there as an assistant under the influence of Professors Regaud and Lacassagne, and of Dr. Coutard. In 1936, he became Head of the Radiotherapy and Radiodiagnosis Department and held that position until 1961.

Since then, he transferred his medical activities to the American Hospital in Paris.

In his numerous articles (more than 100) and some monographs he published during his long career, Dr. Baclesse dealt with various subjects both in the field of radiodiagnosis and radiotherapy. His first interest was in the anatomo-clinical study of head and neck tumors, then in 1937 and 1960, he published excellent monographs about the anatomo-topographic and radiologic study of malignant tumors of the pharnyx and larynx.

It was inspiring to see him reading a roentgenogram of the larynx or, better, of the skull base. He was gifted in projecting into space, to recreate a volume and a reality from a flat surface. His clinical and radiologic knowledge of pharynx and larynx tumors was such that he had been assigned to the Tumor Classification Committee of the World Health Organization.

Another part of his important work comprised radiotherapy of cancerous tumors, especially of the head and neck, uterus, and breast. He was one of the first to obtain cures with radiotherapy alone in breast carcinomas, although they are considered radioresistant. His numerous publications in this respect are well known throughout the world. Less known are his efforts in treating such radioresistant tumors as melanomas, cylindromas, osteogenic sarcomas, and others.

Dr. Baclesse was convinced of the advantages of an association of radiotherapy and surgery and he applied this method to many cancers: head and neck cancers, breast cancers, osteogenic sarcomas, etc. He conceived this association as consisting of "high dose" radiotherapy or cobalt 60 teletherapy, and surgical removal, carried out either systematically, or only if requested in the case of nonsterilization or progressive increase of the cancer.

He was an ardent student of radiotherapeutic techniques and the fractionation problem was his very particular passion. When he joined the Fondation Curie, radiation treatments were short, not exceeding 13 or 14 days; in 1936, he changed these over-all times, increasing them to 6, 8 and even 10 weeks for very advanced or radioresistant cancers. With cobalt 60 teletherapy the over-all time was decreased to 6 or 8 weeks—a method presently used by nearly all anticancer centers.

The contributions of Dr. Baclesse have been numerous and international in attainment. One can say unhesitatingly that without him anticancerous radiotherapy would not be what it is today.

Dr. Baclesse had many honors bestowed upon him. Among these was his Honorary Membership in the American Radium Society.

In the name of his friends and his students, who have admired his warm personality culminating in great friendship, who have liked his teaching, and who have been able to appreciate the charm and the intimacy of his home, we express to Mrs. Baclesse and her children the deep sorrow we feel, with our most sincere sympathy.

Robert Calle, M.D.

Fondation Curie
26, rue d'Ulm
Paris 5e, France

NEWS ITEMS

NINTH INTER-AMERICAN CONGRESS OF RADIOLOGY

The meeting of the Ninth Inter-American Congress of Radiology was held at Hotel San Rafael, Punta del Este, Uruguay, December 6–12, 1967.

The parent institution of these Congresses is the Inter-American College of Radiology.

The Council of the Inter-American College of Radiology elected the following new officers for the next quadrennium (1967–1971): *President:* Juan A. del Regato, M.D., Colorado Springs, Colorado; *Secretary:* F. Bloedorn, M.D., Boston, Massachusetts; and *Treasurer:* M. Vuksanovic, M.D., Miami, Florida.

The College granted the following awards:

Silver Medal: Dr. Félix E. Leborgne, Uruguay, and Dr. Jorge De la Flor, Perú.

Gold Medal: Dr. Philip J. Hodes, Philadelphia, USA, and Dr. Juan A. del Regato, Colorado Springs, USA.

Dr. Guillermo Pezet, Lima, Perú, was commended for his excellent work as the distinguished Editor of the *Revista Interamericana de Radiología*, the official organ of the College, and was reappointed for the next quadrennium.

The Tenth Inter-American Congress of Radiology will be held in San Juan, Puerto Rico, in 1971.

SECOND INTERNATIONAL CONFERENCE ON MEDICAL PHYSICS

The Second International Conference on Medical Physics will be held at the Sheraton-Boston Hotel, Boston, Mass., August 10–14, 1969, under the sponsorship of the U. S. National Committee for Medical Physics and the International Organization for Medical Physics.

The Conference will include symposia and proferred papers on many aspects of medical physics of significance in radiology and nuclear medicine and also on the broader aspects of physics in medicine.

The officers for the Conference are: *President:* Dr. Lauriston S. Taylor; *Honorary President:* Dr. Edith H. Quimby; *Secretary-General:* Dr. Edward W. Webster; *Treasurer:* Dr. Marvin M. D. Williams.

The preliminary program will be available in June 1968.

For further details please write Dr. Edward W. Webster, Secretary-General, Department of Radiology, Massachusetts General Hospital, Boston, Massachusetts 02114.

TENTH INTERNATIONAL CANCER CONGRESS

The Tenth International Cancer Congress will be held in Houston, Texas, USA, May 22–29, 1970.

Under the auspices of the Unio Internationalis Contra Cancrum (U.I.C.C.) the Congress will feature the following events: Preliminary Special Sessions of the Congress; Congress Lectures; Panel Discussions; Sectional Meetings with Proffered Papers on a Variety of Topics or Subjects; Scientific Exhibits; Commercial Exhibits; and Films.

The following is the National Organizing Committee: R. Lee Clark, M.D., *Chairman;* Murray M. Copeland, M.D., *Secretary General, Tenth Congress.*

The office of the Secretariat is at the University of Texas M. D. Anderson Hospital and Tumor Institute at Houston, 6723 Bertner Avenue, P.O. Box 20465, Astrodome Station, Houston, Texas 77025. Cable Address: CANCONG, Houston, Texas.

THE AMERICAN BOARD OF RADIOLOGY

Dr. H. Dabney Kerr, Secretary of The American Board of Radiology, makes the following announcement:

The deadline for filing applications for the June and December oral examinations in 1968, as well as for the written examina-

tion in Radiology in June 1968, *was* December 31, 1967.

In June 1969 the requirement of a written examination will also apply to those candidates seeking certification in Diagnostic Radiology or in Therapeutic Radiology. Those candidates *not eligible* for the oral examination in these two fields in June 1969 will be required to take a written examination.

The deadline for filing applications for the June and December oral examinations in 1969, as well as for the written examination in Radiology, in Diagnostic Radiology, or in Therapeutic Radiology, in June 1969, is December 31, 1968.

Passing the written examination is a prerequisite to taking the oral examination.

TWENTIETH ANNUAL JOSEPH AND SAMUEL FREEDMAN LECTURES

On Saturday and Sunday, April 6 and 7, 1968, Dr. Heinz S. Weens, Chairman, Department of Radiology, Emory University, Atlanta, Georgia, will deliver the Twentieth Annual Joseph and Samuel Freedman Lectures in Diagnostic Radiology at the University of Cincinnati College of Medicine.

Radiologists desiring to attend are requested to write for further details to Dr. Benjamin Felson, Department of Radiology, Cincinnati General Hospital, Cincinnati, Ohio 45229.

NEW YORK ROENTGEN SOCIETY

The Annual Spring Conference of the New York Roentgen Society will be held at the Waldorf Astoria Hotel, New York, April 25–28, 1968.

The Chairman is Dr. Albert Dunn, Roosevelt Hospital, 428 West 59 Street, New York, New York 10019, and the Scientific Program Chairman is Dr. William Seaman, Columbia Presbyterian Hospital, 622 West 168 Street, New York, New York 10032.

For further information please write to Dr. David H. Baker, M.D., Secretary, Babies Hospital, 3975 Broadway, New York, New York 10032.

ISRAELI CONGRESS OF RADIOLOGY

An Israeli Congress of Radiology will be held in Jerusalem on April 7–9, 1968.

The Annual Leo G. Rigler Lecture will be delivered by Dr. John Hodson of London on April 7.

For further information, please write Dr. Samuel Schorr, Ichalov Hospital, Tel Aviv, Israel.

POSTGRADUATE COURSE IN PEDIATRIC RADIOLOGY

Congenital Heart Disease

A Postgraduate Course on Congenital Heart Disease will be held at the Cornell University Medical College, Memorial Hospital Auditorium, 424 East 68th Street, New York, New York, April 25–27, 1968.

The Guest Faculty includes: Herbert L. Abrams, M.D., Harvard Medical School-Peter Bent Brigham Hospital, Boston, Mass.; Murray G. Baron, M.D., The Mount Sinai Hospital, New York; Sidney Blumenthal, M.D. and Kent Ellis, M.D., Columbia-Presbyterian Medical Center, New York; John A. Campbell, M.D., Indiana University Medical Center, Indianapolis, Ind.; Robert L. DeHaan, Ph.D., Carnegie Institution of Washington, Baltimore; Jessee E. Edwards, M.D., The Charles T. Miller Hospital, Saint Paul, Minn.; Larry P. Elliott, M.D., University of Florida, College of Medicine, Gainesville, Florida; Owings W. Kincaid, M.D., Mayo Clinic, Rochester, Minn.; John A. Kirkpatrick, M.D., Saint Christopher's Hospital for Children, Philadelphia, Pa.; and Richard Van Praagh, M.D., The Children's Hospital Medical Center, Boston, Mass.

Inquiries should be addressed to Herman Grossman, M.D., Department of Radiology, New York Hospital-Cornell Medical Center, 525 East 68th Street, New York, N.Y. 10021.

SYMPOSIUM ON DOSE RATE IN MAMMALIAN RADIATION BIOLOGY

A Symposium on Dose Rate in Mammalian Radiation Biology will be held April 29–May 1, 1968, Oak Ridge, Tennessee.

For information, please write D. G. Brown, at UT-AEC Agricultural Research Laboratory, 1299 Bethel Valley Road, Oak Ridge, Tennessee 37830.

REFRESHER COURSE IN DIAGNOSTIC ROENTGENOLOGY

The Ninth Annual Refresher Course in Diagnostic Roentgenology will be held by the Radiology Department of the University of Cincinnati College of Medicine under the directorship of Dr. Benjamin Felson from June 3–8, 1968.

The course will include, in addition to lectures and demonstrations, teaching methods employing audience participation. Saturday, June 8, will be devoted entirely to radiation physics.

Further information concerning the course, may be obtained by writing to Dr. Harold B. Spitz, Department of Radiology, Cincinnati General Hospital, Cincinnati, Ohio 45229.

THIRD WORKSHOP ON THERMOLUMINESCENT DOSIMETRY

The University of Wisconsin Extension and Medical Center announces a third workshop on thermoluminescent dosimetry to be held at the Wisconsin Center on August 19–21, 1968.

The course will consist of 13 hours of lectures and 8 hours of laboratory work, and is intended to cover the fundamentals of thermoluminescent dosimetry. The enrollment will be limited to forty.

For further information, please contact Dr. John R. Cameron, Department of Radiology, University Hospitals, Madison, Wisconsin 53706.

INTERNATIONAL SYMPOSIUM ON NUCLEAR ELECTRONICS

The Société Française des Electroniciens et des Radioélectriciens announces the forthcoming International Symposium on Nuclear Electronics which it is organizing conjointly with the French Atomic Energy Commission, and which will be sponsored by the big International Agencies, expecially the International Atomic Energy Agency.

The meeting will be held in the Palais des Congrès at Versailles, France, September 10–13, 1968. It will be devoted to the electronics associated with experimentation in the field of nuclear and corpuscular physics.

The President of The Organizing Committee is Mr. Henri Angles D'Auriac.

Address: Boîte Postale n° 17–78 Chatou, France.

FIRST INTERNATIONAL SYMPOSIUM ON DETECTION OF CANCER

The First International Symposium on Detection of Cancer will be held at SPA (Belgium), September 26–29, 1968.

The Chairman of the Organizing Committee is Dr. Henri Ramioul, Civil Hospital of Verviers.

The purpose of the Symposium is discussion of the various problems in detection of gynecologic cancer, breast cancer, digestive cancer and pulmonary cancer.

There will also be Round Table Discussions, Scientific Exhibits, and a Recreational Program.

Registrations are accepted at the Secrétariat Général, Quai du Barbou, 4, Liège, Belgium.

For further particulars, please contact the Secretary of the Organizing Committee: Doctor Albert Liegeois, Civil Hospital of and in Verviers.

BOOK REVIEWS

Books sent for review are acknowledged under: Books Received. This must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interest of our readers as space permits.

Diagnostic Radiology. Edited by Prof. Luigi Turano, Direttore dell'Istituto di Radiologia dell'Università di Roma. Volume IV. The Gastro-intestinal Tract, by Prof. Cesare Colosimo. In Italian. Cloth. Pp. 826, with 927 illustrations. Unione Tipografico-Editrice Torinese, 1967.

This is the fourth volume of the Italian series on Diagnostic Radiology edited by Prof. Turano and is a truly excellent dissertation on the gastrointestinal tract. Prof. Colosimo writes easily and is obviously at home with his assignment and with the vast literature on gastrointestinal radiology. The most remarkable feature of this book is the emphasis placed on the anatomic, physiologic and pathologic basis for the radiologic findings. This is extremely helpful for the formation of basic concepts on the part of the radiologic trainees.

The book is organized in a conventional manner and describes in detail the physical and psychological preparation of the patient, the techniques which need to be mastered, the disease entities that can be encountered and the differential diagnostic features in the various parts of the gastrointestinal tract, beginning with the pharynx and ending with the rectum.

Extensive bibliographies follow each of the 13 chapters, and one cannot help but be impressed by the familiarity of the author with main works published in several languages.

The illustrations are excellent and numerous, and the printing is clear.

This fourth volume of the series is in every way as good as the volumes already published, and Prof. Colosimo must be congratulated on his work.

This extensive treatise on Radiology by Prof. Turano will undoubtedly become the basic text for the Italian training centers.

Cesare Gianturco, M.D.

Roentgenologic Diagnosis. A Complement in Radiology to the Beeson and Mc Dermott Textbook of Medicine. Volume 1. By J. George Teplick, M.D., Clinical Associate Professor of Radiology, Hahnemann Medical College; Marvin E. Haskin, M.D., F.A.C.P., Clinical Assistant Professor of Radiology, Hahnemann Medical College; and Arnd P. Schimert, M.D., Formerly Associate Professor of Radiology, Hahnemann Medical College. Cloth. Pp. 527, with many illustrations. Price, $38.00 for set of two Volumes. W. B. Saunders Company, West Washington Square, Philadelphia, Pa. 19105, 1967.

This volume, the first of two, is meant to be used in conjunction with the Beeson and Mc Dermott "Textbook of Medicine," known to so many of us as Cecil and Loeb. The aims, organization and limitations of this work must be understood to appreciate its value.

The book is not a systematic text of Radiology. It is rather a ". . . concise but comprehensive survey of the radiographic findings associated with most of some eight hundred diseases as discussed in . . ." Beeson and McDermott's Textbook. As such, the organization of the book follows the plan of the medical text. At times, this is illogical relative to the thought processes of problem solving that face the specialist in Radiology. There is very little information concerning differential diagnosis from radiographic findings. An excellent index makes up for this failing in part.

The descriptions of disease processes are terse, and almost exclusively limited to radiologic aspects. The bibliography appended to each section is unusually fine and points to additional literature where more detailed information can be found.

It is very easy to criticize individual segments of as broad a work as this. For example, the single illustration of the angiocardiographic appearance of tetralogy of Fallot is not illustrative of the anatomic changes in the infundibulum of the right ventricle. Another example concerns the section on anomalous coronary artery arising from the pulmonary artery. The statement that this lesion ". . . is usually most adequately opacified during selective angiocardiography . . ." is incorrect. (The best way to opacify the anomalous vessel is by selective thoracic aortography with injection into the contralateral—right—coronary artery. The

flow in the anomalous—left—coronary artery is almost always reversed and directed toward the pulmonary artery.)

Such objections are minor and do not seriously detract from the worth of the book. A more important reservation is that only diseases discussed in the parent text and their related radiologic procedures are presented. (For example, there is no reference to mammography, since the "Textbook of Medicine" does not discuss primary carcinoma of the breast.)

Consequently, the book will be of most value for the internist and, particularly, for medical students. It is especially recommended to them. For the resident in Radiology and for radiologists in practice, the book is also useful within the limitations the authors clearly indicate. The volume is lavishly illustrated, and the reproductions are of excellent quality. The reviewer expects to obtain a copy of the second volume, when it becomes available.

Richard G. Lester, M.D.

BOOKS RECEIVED

Basic Radiation Biology. By Donald J. Pizzarello, Ph.D., Associate Professor of Radiology (Radiation Biology); and Richard L. Witcofski, Ph.D., Assistant Professor of Radiology (Medical Physics), The Bowman Gray School of Medicine, Wake Forest University, Winston-Salem, N. C. Cloth. Pp. 301, with some figures. Price, $9.50. Lea & Febiger, 600 Washington Square, Philadelphia, Pa. 19106, 1967.

La Cronobiodose in Radioterapia: Dose, Tempo, Volume. By Dott. Prof. Franco Bistolfi, Assistente Ordinario dell'Istituto di Radiologia, dell'Università di Genova. Cloth. Pp. 658, with some illustrations. Price, L. 30,000. Piccin Editore, Via Porciglia 10, Padova, Italy, 1967.

Principles of Nuclear Medicine. Edited by Henry N. Wagner, Jr., M.D., Professor of Radiological Science; Associate Professor of Medicine, The Johns Hopkins Medical Institutions. Cloth. Pp. 896, with some illustrations. Price, $27.50. Canadian price, $29.70. W. B. Saunders Company, West Washington Square, Philadelphia, Pa. 19106, 1968.

Histologic Patterns in Tumor Pathology. By Mark E. Williamson, M.D., Instructor, Department of Pathology, University of Colorado Medical Center, Denver; Jan E. Leestma, M.D., Instructor, Department of Pathology, University of Colorado Medical Center, Denver; William C. Black, III, M.D., Instructor in Pathology, Washington University School of Medicine, St. Louis; and Donald West King, M.D., Francis Delafield Professor and Chairman, Department of Pathology, College of Physicians and Surgeons, Columbia University, New York. Cloth. Pp. 212, with 191 illustrations. Price, $16.00. Hoeber Medical Division, Harper & Row, 49 East 33rd Street, New York, N. Y. 10016, 1967.

Cardiac Radiology. By Edward F. Dunne, M.B., B.Ch., Department of Radiology, St. Vincent's Hospital, Los Angeles, Calif. Cloth. Pp. 256, with 152 figures. Price, $12.50. Lea & Febiger, 600 S. Washington Square, Philadelphia, Pa. 19106, 1967.

An Atlas of Pathologic Pneumoencephalographic Anatomy. By Giovanni di Chiro, M.D., Head of Section on Neuroradiology, National Institute of Neurological Diseases and Blindness, National Institutes of Health, Bethesda, Md.; with contributions by Mannie M. Schechter, M.D., and Ingmar Wickbom, M.D. Cloth. Pp. 555, with many illustrations. Price, $49.50. Charles C Thomas, Publisher, 301–327 East Lawrence Avenue, Springfield, Ill. 62703, 1967.

The Management of Trauma. By members of the staff of the Johns Hopkins University School of Medicine and the Johns Hopkins Hospital. Edited by Walter F. Ballinger, II, M.D., Formerly Associate Professor of Surgery, The Johns Hopkins University School of Medicine, Baltimore; Bixby Professor and Chairman, Department of Surgery, Washington University School of Medicine, St. Louis; Surgeon-in-Chief, Barnes Hospital, St. Louis; Robert B. Rutherford, M.D., Assistant Professor of Surgery, The Johns Hopkins University School of Medicine; Surgeon-in-Charge, Emergency Service, The Johns Hopkins Hospital; and George D. Zuidema, M.D., Professor and Director, Department of Surgery, The Johns Hopkins University School of Medicine; Surgeon-in-Chief, The Johns Hopkins Hospital. Cloth. Pp. 815, with many illustrations. Price, $25.00. Canadian price $27.00. W. B. Saunders Company, West Washington Square, Philadelphia, Pa. 19106, 1968.

Progress in Lymphology. Proceedings of the International Symposium on Lymphology, Zurich, Switzerland, July 19–23, 1966. Edited by A. Rüttimann, Zurich. Cloth. Pp. 426, with many illustrations. Price, DM 148.-. ($37.00). Georg Thieme Verlag, Stuttgart. Distributed in the U.S.A. and Canada by Hafner Publishing Company, New York, N. Y. 10003, 1967.

Angiographie des Hirnkreislaufs. By Prof. Dr. Kurt Decker, Nervenklinik der Universität München; and Dr. Herbert Backmund, Max-Planck-Institut für Psychiatrie, München. Cloth. Pp. 76, with many illustrations. Price, DM 44.-. Georg Thieme Verlag, Stuttgart. In U.S.A. and Canada, Intercontinental Medical Book Corporation, New York, N. Y. 10016, 1968.

Echoenzephalographie. By H. W. Pia, Prof. Dr. med., Direktor der Neurochirurgischen Universitätsklinik Giessen; and C.-L. Geletneky, Dr. med. wissenschaftlicher Assistent und der Neurochirurgischen Universitätsklinik Giessen. Cloth. Pp. 168, with many illustrations. Price, DM 59.-. ($14.75). Georg Thieme Verlag, Stuttgart. In the U.S.A. and Canada, Intercontinental Medical Book Corporation, New York, N. Y. 10016, 1967.

SOCIETY PROCEEDINGS

MEETINGS OF RADIOLOGICAL SOCIETIES*

UNITED STATES OF AMERICA

AMERICAN ROENTGEN RAY SOCIETY
Secretary, Dr. Ted F. Leigh, Emory University Clinic, Atlanta, Ga. 30322. Annual Meeting: Jung Hotel, New Orleans, La., Oct. 1–4, 1968.

AMERICAN RADIUM SOCIETY
Secretary, Dr. Fernando G. Bloedorn, Division of Radiotherapy, University of Maryland Hosp., Baltimore, Md. 21201. Annual meeting: Hotel Fontainebleau, Miami Beach, Fla., April 7–11, 1968.

RADIOLOGICAL SOCIETY OF NORTH AMERICA
Secretary-Treasurer, Dr. Maurice Doyle Frazer, 1744 South Fifty-eighth St., Lincoln, Neb. Annual meeting: Palmer House, Chicago, Ill., Dec. 1–6, 1968.

AMERICAN COLLEGE OF RADIOLOGY
Executive Director, William C. Stronach, 20 N. Wacker Drive, Chicago 6, Ill. Annual meeting to be announced.

SECTION ON RADIOLOGY, AMERICAN MEDICAL ASSOCIATION
Secretary, Dr. Kenneth L. Krabbenhoft, Harper Hospital, Detroit, Mich. 48201. Annual meeting: San Francisco, Calif., June 16–20, 1968.

AMERICAN BOARD OF RADIOLOGY
Secretary, Dr. H. Dabney Kerr. Correspondence should be directed to Kahler Hotel Building, Rochester, Minn.

The Spring 1968 oral examination will be held at the Fontainebleau Hotel, Miami Beach, Florida, June 10–14, inclusive. The deadline for filing applications was December 31, 1967. Candidates eligible for this examination will not be required to take the written examination.

The first written examination will be held the latter half of June 1968 in various centers of the country for all residents having completed 3 years of approved training as of June 30, 1968. Deadline for filing for this examination and the oral examination of December 1968 was December 31, 1967.

AMERICAN ASSOCIATION OF PHYSICISTS IN MEDICINE
Secretary, Leonard Stanton, Hahnemann Medical College, 230 N. Broad St., Philadelphia, Pa. 19102. Annual meeting to be announced.

AMERICAN SOCIETY OF THERAPEUTIC RADIOLOGISTS
Secretary, Dr. J. A. del Regato, Penrose Cancer Hospital, Colorado Springs, Colo. 80907.

AMERICAN SOCIETY FOR DIAGNOSTIC ULTRASOUND
Secretary, Dr. Charles C. Grossman, 552 N. Neville St., Pittsburgh, Pa. 15213.

TWELFTH INTERNATIONAL CONGRESS OF RADIOLOGY
President, Dr. Kempo Tsukamoto, 9-1, 4-chome, Angewa, Chiba, Japan. Meeting: Hotel New Otane, Tokyo, Japan, Oct. 6–11, 1969.

TENTH INTER-AMERICAN CONGRESS OF RADIOLOGY
Counselor for the United States, Dr. Juan A. del Regato, Penrose Cancer Hospital, 2215 North Cascade Ave., Colorado Springs, Colo. 80907.
President, Dr. Juan A. del Regato, Colorado Springs, Colo., USA.
Secretary, Dr. F. Bloedoon, Boston, Mass., USA.
Meeting: San Juan, Puerto Rico, 1971.

INTER-AMERICAN COLLEGE OF RADIOLOGY
President, Dr. Oscar Soto, H. Urteaga 480, Lima, Perú.

ALABAMA RADIOLOGICAL SOCIETY
Secretary, Dr. Walter Brower, Birmingham, Ala. Meets time and place of Alabama State Medical Association.

ALASKA RADIOLOGICAL SOCIETY
Secretary, Dr. Bruce C. Wright, Providence Hospital, Anchorage, Alaska. Meets third Wednesday each month.

ARIZONA RADIOLOGICAL SOCIETY
Secretary-Treasurer, Dr. Robert E. Steyskal, 550 W. Thomas Rd., Phoenix, Ariz. 85013. Two regular meetings a year. Annual meeting at time and place of State Medical Association and interim meeting six months later.

ARKANSAS CHAPTER OF AMERICAN COLLEGE OF RADIOLOGY
Secretary-Treasurer, Dr. William J. Rhinehart, St. Vincent Infirmary, Little Rock, Ark. 72205.

ARKANSAS RADIOLOGICAL SOCIETY
Secretary, Dr. Charles W. Anderson, 1108½ Poplar, Pine Bluff, Ark. Meets every three months and also at time and place of State Medical Association.

ASSOCIATION OF UNIVERSITY RADIOLOGISTS
Secretary-Treasurer, Dr. Harry Z. Mellins, S.U.N.Y. College of Medicine, Brooklyn, New York 11201. Annual Meeting: Ohio State University School of Medicine, Columbus, Ohio, May 9–11, 1968.

ATLANTA RADIOLOGICAL SOCIETY
Secretary, Dr. Donald R. Rooney, Burnt Hickory Road, Marietta, Ga. Meets monthly except during three summer months, on third Tuesday, at the Academy of Medicine, Atlanta, Ga., at 8:00 P.M.

BAVARIAN-AMERICAN RADIOLOGIC SOCIETY
Secretary, Colonel Kurt Harrell, Landstuhl Army Medical Center, Landstuhl, Germany. Meets quarterly.

BLOCKLEY RADIOLOGICAL SOCIETY
Secretary-Treasurer, Dr. R. John Gould, 41 Lombardy Rd., Drexel Hill, Pa. 19026.

BLUEGRASS RADIOLOGICAL SOCIETY
Secretary-Treasurer, Dr. Joe Bernard, Central Baptist Hosp., Lexington, Kentucky 40503. Meets quarterly.

BROOKLYN RADIOLOGICAL SOCIETY
Secretary, Dr. Skottowe DePass, 69-13 Forest Ave., Brooklyn, N. Y. 11227. Meets first Thursday of each month, October through June.

BUFFALO RADIOLOGICAL SOCIETY
Secretary, Dr. Richard Sheehan, 36 Briarlee Drive, Tonawanda, N. Y. Meets second Monday evening each month, October to May inclusive.

CALIFORNIA RADIOLOGICAL SOCIETY
Secretary, Dr. James J. McCort, Santa Clara Valley Med. Ctr., San Jose, Calif. Meets annually during meeting of California Medical Association.

CATAWBA VALLEY RADIOLOGICAL SOCIETY
Secretary, Dr. Emmett R. White, P. O. Box 303, Rutherford College, N. C. 28671. Meets every Friday, Dept. of Radiology, Valdese General Hosp., Valdese, N. C., at 12:00 NOON.

CENTRAL NEW YORK RADIOLOGICAL SOCIETY
Secretary-Treasurer, Dr. Robert A. Bornhurst, State Univ. Hospital, 750 E. Adams St., Syracuse, N. Y. 13210. Meets first Monday each month, October through May.

CENTRAL OHIO RADIOLOGICAL SOCIETY
Secretary, Dr. Ollie E. Southard, 2787 Tudor Rd., Columbus, O. 43209. Meets second Thursday in October, November, January, and March 15 and May 19 at Fort Hayes Hotel, Columbus, Ohio.

CHICAGO ROENTGEN SOCIETY
Secretary-Treasurer, Dr. Fredric D. Lake, 2548 N. Lakeview Ave., Chicago, Ill. 60614. Meets second Thursday of each month, October to April, except December, at the Pick-Congress Hotel at 8:00 P.M.

CLEVELAND RADIOLOGICAL SOCIETY
Secretary-Treasurer, Dr. Theodore J. Castele, 18869 Canyon Rd. Parkview Park, Ohio 44126. Meetings at 7:00 P.M. on fourth Monday of October, November, January, February, March and April.

*** Secretaries of societies are requested to send timely information promptly to the Editor.**

Colorado Radiological Society
Secretary, Dr. Charles E. Seibert, Denver Gen. Hosp., Denver, Colo. 80218. Meets third Friday of each month at Denver Athletic Club from September through May.

Connecticut Valley Radiologic Society
Secretary, Dr. William W. Walthall, Jr., 130 Maple St., Springfield, Mass. Meets in April and October.

Dallas-Fort Worth Radiological Society
Secretary-Treasurer, George E. Plum, 712 N. Washington Ave., Dallas, Tex. 75246. Meets monthly, third Monday, at Southwest International Airport at 6:30 P.M.

Detroit Roentgen Ray and Radium Society
Secretary, Dr. Robert L. Willis, Harper Hospital, Detroit, Mich. 48201. Meets monthly, first Thursday, October through May, at David Whitney House, 1010 Antietam, at 6:30 P.M.

East Bay Radiological Society
Secretary, Dr. Tom H. Piatt, 12 Camino Encinas, Orinda, Calif. 94563. Meets first Thursday each month, Oct. through May, at University Club, Oakland, Calif.

East Tennessee Radiological Society
Secretary-Treasurer, Dr. T. F. Haase, Jr., 205 Medical Arts Building, Knoxville, Tenn. Meets in January and September.

Florida Radiological Society
Secretary, Dr. John C. Jowett, Orlando, Fla. Meets twice annually, in the spring with the annual State Society Meeting and in the fall.

Florida West Coast Radiological Society
Secretary-Treasurer, Allen M. Sheer, 501 E. Buffalo Ave., Tampa, Fla. 33603. Meets in January, March, May, July, September and November.

Georgia Radiological Society
Secretary, Dr. J. L. Clements, Jr., 134 LaGrange St., Newman, Georgia 30263. Meets in spring and fall with Annual State Society Meeting.

Greater Cincinnati Radiological Society
Secretary-Treasurer, Dr. Owen L. Brown, 2421 Auburn Ave., Cincinnati, Ohio 45219.

Greater Louisville Radiological Society
Secretary-Treasurer, Dr. L. D. LeNeave, 315 E. Broadway, Louisville, Ky. 40202. Meets monthly.

Greater Miami Radiological Society
Secretary Treasurer, Dr. Thomas W. Tufts, Broward General Hospital, 1600 S. Andrews Ave., Ft. Lauderdale, Fla. Meets monthly, third Wednesday at 8:00 P.M., at Jackson Memorial Hospital, Miami, Fla.

Greater St. Louis Society of Radiologists
Secretary-Treasurer, Dr. Alexander J. Link, 7215 Maryland, St. Louis, Mo. 63130.

Hawaii Radiological Society
Secretary-Treasurer, Dr. R. K. Wang, P.O. Box 256, Wahiawa, Oahu 96786. Meets third Monday of each month at 7:30 P.M.

Health Physics Society
Secretary, John W. Thomas, Philadelphia, Pa. Annual Meeting: Denver-Hilton Hotel, Denver, Colo., June 16–20, 1968.

Houston Radiological Society
Secretary, Dr. Thomas S. Harle, 1200 Moursond Drive, Houston, Tex. 77025. Meets fourth Monday of each month, except June, July, August and December, at the Doctors' Club, 8:00 P.M., Houston, Tex.

Idaho State Radiological Society
Secretary, Dr. George H. Harris, Bannock Memorial Hospital, Pocatello, Idaho. Meets in the spring and fall.

Illinois Radiological Society
Secretary, Dr. George A. Miller, Carle Hospital Clinic, Urbana, Ill. Meets in the spring and fall.

Indiana Roentgen Society, Inc.
Secretary, Dr. Edwin F. Koch, Jr., 915 University Ave., Muncie, Ind. 47303. Meets first Sunday in May and during fall meeting of Indiana State Medical Association.

Iowa Radiological Society
Secretary, Dr. L. L. Maher, 1419 Woodland Ave., Des Moines, Iowa. Luncheon and business meeting during annual session of Iowa State Medical Society. The scientific section is held in the autumn.

Kansas Radiological Society
Secretary-Treasurer, Dr. Robert C. Lawson, 310 Medical Arts Bldg., 10th and Horne, Topeka, Kan. Meets in spring with State Medical Society and in winter on call.

Kentucky Chapter, American College of Radiology
Secretary-Treasurer, Dr. Ralph C. Quillin, 1221 S. Broadway, Lexington, Ky. 40504. Meets in April and September.

Kings County Radiological Society
Secretary, Dr. Sidney Hendler, 1880 Ocean Ave., Brooklyn 30, N. Y. Meets Kings County Med. Soc. Bldg. monthly on fourth Thursday, October to May, 8:45 P.M.

Knoxville Radiological Society
Secretary, Dr. Clifford L. Walton, Blount Professional Bldg., Knoxville 20, Tenn. Meetings are held the third Monday of every other month at the University of Tennessee Memorial Research Center and Hospital.

Long Island Radiological Society
Secretary, Dr. Robert J. Hochstim, 1200 Stewart Ave., Garden City, N. Y. 11533. Meets monthly.

Los Angeles Radiological Society
Secretary, Dr. Harvey I. Meyers, 2010 Wilshire Blvd., Los Angeles, Calif. 90057. Meets second Wednesday of month in September, November, January, April and June at Los Angeles County Medical Association Building, Los Angeles, Calif.

Louisiana-Texas Gulf Coast Radiological Society
Secretary-Treasurer, Dr. Edward A. Sheldon, 109 Doctors Bldg., Beaumont, Texas 77701.

Maine Radiological Society
Secretary-Treasurer, Dr. Robert A. Bearor, Maine Medical Center, Portland, Maine 04102. Meets in June, September, December and April.

Maryland Radiological Society
Secretary, Dr. Henry Startzman, Medical Arts Building, Baltimore, Md.

Memphis Roentgen Society
Secretary-Treasurer, Dr. Vernon I. Smith, Jr., Suite 203, 1085 Madison Ave., Memphis, Tenn. 38104. Meets first Monday of each month at John Gaston Hospital.

Miami Valley Radiological Society
Secretary, Dr. Darwood B. Hance, Reid Memorial Hospital, Richmond, Indiana. Meets third Thursday of fall, winter and spring months at 7:30 P.M. at Miami Valley Hospital, Dayton, Ohio.

Mid-Hudson Radiological Society
Secretary-Treasurer, Dr. Herbert S. Berlin, Hopewell Junction, N. Y. Meets 7:00 P.M., first Wednesday of each month, September to May.

Milwaukee Roentgen Ray Society
Secretary-Treasurer, Dr. James E. Bell, 8700 W. Wisconsin Ave., Milwaukee, Wis. 53213. Meets monthly on fourth Monday, October through May, at University Club.

Minnesota Radiological Society
Secretary-Treasurer, Dr. Edward A. Peterson, 572 Lowry Medical Arts Bldg., St. Paul, Minn. Meets twice annually, fall and winter.

Mississippi Radiological Society
Secretary-Treasurer, Dr. Dan T. Keel, Jr., 504 Chippewa St., Brookhaven, Miss. Meets third Thursday of each month at the Heidelberg Hotel, Jackson, at 6:00 P.M.

Missouri Radiological Society
Secretary-Treasurer, Dr. Harold B. Rapp, Cape Girardeau, Mo.

Montana Radiological Society
Secretary, Dr. Clark Grimm, Great Falls, Montana. Meets at least once a year.

Nebraska State Radiological Society
Secretary-Treasurer, Dr. Otto A. Troester, 924 Sharp Building, Lincoln, Nebraska 60508. Meets third Wednesday of each month at 6 P.M. in Omaha or Lincoln.

Nevada Radiological Society
Secretary, Dr. William G. Arbonies, Department of Radiology, St. Mary's Hospital, Reno, Nev.

New England Roentgen Ray Society
Secretary, Dr. Morris Simon, 330 Brookline Ave., Boston, Mass. 02153. Meets third Friday of each month, October through May, at The Longwood Towers, 20 Chapel Street, Brookline, Mass., at 4:30 P.M.

New Hampshire Roentgen Ray Society
Secretary, Dr. Paul Y. Hasserjian, 1470 Elm St., Manchester, N. H. Meets four to six times yearly.

New Mexico Association of Radiologists
Secretary-Treasurer, Dr. Justin J. Wolfson, Department of Radiology, Bernalillo County-Indian Hospital, Albuquerque, New Mexico.

New Mexico Society of Radiologists
Secretary, Dr. Phil Fox, Albuquerque, New Mexico. Four meetings annually, three held in Albuquerque, N. M., and one held at time and place of New Mexico State Medical Society annual meeting.

New York Roentgen Society
Secretary, Dr. David H. Baker, Babies Hospital, 3975 Broadway, New York, N. Y. 10032. Meets monthly on third Monday at the New York Academy of Medicine at 4:30 P.M. Annual meeting: April 25–28, 1968.

North Carolina Chapter of ACR.
Secretary-Treasurer, Dr. Ira Bell, Hickory, N. C. Annual meeting to be announced.

North Carolina Radiological Society
Secretary, Dr. E. H. Schultz, North Carolina Memorial Hospital, Chapel Hill, N. C. Meets in the spring and fall each year.

North Dakota Radiological Society
Secretary, Dr. A. Ohrt, 408 Medical Arts Bldg., Fargo, N. D. 58102. Meets at time of State Medical Association meeting. Other meetings arranged on call of the President.

North Florida Radiological Society
Secretary, Dr. Charles H. Newell, 800 Miami Road, Jacksonville 7, Fla. Meets quarterly in March, June, September and December.

Northeastern New York Radiological Society
Secretary, Dr. Anthony J. Tabacco, 621 Central Ave., Albany 6, N. Y. Meets in Albany area on second Wednesday of October, November, March and April.

Northern California Radiological Society
Secretary-Treasurer, Ivan D. Siddons, 3701 J. St., Suite 106, Sacramento, Calif. 95816. Meets fourth Monday of Sept., Nov., Jan., March and May at the Sutter Club in Sacramento.

Northwestern Ohio Radiological Society
Secretary, Dr. Vito J. Zupa, Mercy Hospital, Department of Radiology, Toledo, Ohio.

Ohio State Radiological Society
Secretary, Dr. Robert D. Berkebile, Elyria Memorial Hospital, Elyria, Ohio 44035.

Oklahoma State Radiological Society
Secretary, Dr. Donald F. Mauritson, 100 Utica Square Med. Center, Tulsa, Okla. 74114. Meets in January, May and October.

Orange County Radiological Society
Secretary, Dr. George W. Logan, 301 Newport Blvd., Newport Beach, Calif. Meets fourth Tuesday of every month at Orange County Medical Association Building.

Oregon Radiological Society
Secretary-Treasurer, Dr. Irving J. Horowitz, 2311 N.W. Northrup Str., Portland, Ore. 97210. Meets on second Wednesday of month, October through April, at the University Club, Portland, Ore.

Orleans Parish Radiological Society
Secretary, Dr. Joseph V. Schlosser, Charity Hospital, New Orleans 13, La. Meets second Tuesday of each month.

Pacific Northwest Radiological Society
Secretary-Treasurer, Dr. Willis Taylor, 1118 9th Ave., Seattle, Washington. Annual meeting to be announced.

Pennsylvania Radiological Society
Secretary, Dr. T. Frederick Weiland, 619 Ridgeway Ave., Grove City, Pa. 16127. Annual meeting to be announced.

Philadelphia Roentgen Ray Society
Secretary, Dr. C. Jules Rominger, Misericordia Hospital, 54th St. and Cedar Ave., Philadelphia, Pa. 19143. Meets first Thursday of each month at 5 P.M., from October to May in Thompson Hall, College of Physicians.

Pittsburgh Roentgen Society
Secretary, Dr. Edward R. Seitz, 601 Jenkins Bldg., Pittsburgh, Pa. 15222. Meets second Wednesday of month, October through June, at Park Schenley Restaurant.

Radiological Society of Connecticut, Inc.
Secretary-Treasurer. Dr. Henry J. Fox, 10 Washington Ave., Bridgeport, Conn. Meetings are held quarterly.

Radiological Society of Greater Cincinnati
Secretary-Treasurer, Dr. Donald E. Gunderson, 3553 Bayard Dr., Cincinnati, Ohio 45208. Meets first Monday of each month at Cincinnati Academy of Medicine.

Radiological Society of Greater Kansas City
Secretary, Dr. J. Stewart Whitmore, 1010 Rialto Bldg., Kansas City, Mo. Meets last Friday of each month.

Radiological Society of Kansas City
Secretary, Dr. Arthur B. Smith, 800 Argyle Bldg., Kansas City, Mo. Meets third Thursday of each month.

Radiological Society of Louisiana
Secretary, Dr. Lester W. Eavenson, 2700 Napoleon Ave., New Orleans 15, La. Meets semiannually, during Louisiana State Medical Society meeting and 6 months later.

Radiological Society of New Jersey
Secretary, Dr. John W. Marquis, 12 Hawthorne Ave., East Orange, N. J. 07018. Meets in Atlantic City at time of State Medical Society meeting and in October or November in Newark, N. J.

Radiological Society of Rhode Island
Secretary-Treasurer, Dr. John M. Vesey, 1196 Elmwood Ave., Cranston, R. I.

Radiological Society of South Dakota
Secretary-Treasurer, Dr. Donald J. Peik, 303 S. Minnesota Ave., Sioux Falls, S. D.

Radiological Society of Southern California
Secretary-Treasurer, Dr. Robert G. Williams, The Santa Barbara Medical Clinic, P.O. Box 1200, Santa Barbara, Calif. 93102. Meets three times a year, usually October, February and May.

Radiological Society of the State of New York
Secretary-Treasurer, Dr. John W. Colgan, 273 Hollywood Ave., Rochester 18, N. Y.

Redwood Empire Radiological Society
Secretary, Dr. Lee F. Titus, 164 W. Napa St., Sonoma, Calif. Meets second Monday every other month.

Richmond County Radiological Society
Secretary, Dr. W. F. Hamilton, Jr., University Hospital, Augusta, Ga. Meets first Thursday of each month at various hospitals.

Rochester Roentgen Ray Society, Rochester, N. Y.
Secretary, Dr. Kenneth E. Robinson, Rochester General Hospital, 1425 Portland Ave., Rochester, N. Y. 14621. Meets at 8:15 P.M. on the last Monday of each month, September through May, at Strong Memorial Hospital.

Rocky Mountain Radiological Society
Secretary-Treasurer, Dr. Robert W. Lackey, 4200 E. Ninth Ave., Denver, Colo. Annual meeting: Brown Palace Hotel, Denver, Colo., Aug. 15–17, 1968.

San Antonio-Military Radiological Society
Secretary, Dr. Hugho F. Elmendorf, Jr., 730 Medical Arts Bldg., San Antonio 5, Tex. Meets third Wednesday of each month in Fort Sam Houston Officer's Club at 6:30 P.M.

San Diego Radiological Society
President-Secretary, Charles R. Henkelmann, 3909 Palm Drive, Bonita, Calif. 92002. Meets first Wednesday of each month at the Town & Country Motel.

San Francisco Radiological Society
Secretary, Dr. H. Joachim Burhenne, Children's Hospital and Adult Medical Center, 3700 California St., San Francisco, Calif. 94119. Meets quarterly at the San Francisco Medical Society, 250 Masonic Ave., San Francisco, Calif. 94118.

Santa Clara County Radiological Society
Secretary, Dr. D. Brendan O'Donnell, 696 E. Santa Clara St., San Jose, Calif. 95112. Meets monthly at the Santa Clara County Medical Association Bldg., 700 Empey Way, San Jose, Calif.

Section on Radiology, California Medical Association
Secretary, Dr. William H. Graham, 630 East Santa Clara St., San Jose, Calif.

Section on Radiology, Medical Society of the District of Columbia
Secretary-Treasurer, Dr. Louis Wener, Cafritz Memorial Hosp., 1310 Southern Ave., S.E., Washington, D. C. 20032. Meets at Medical Society Library, third Wednesday of January, March, May and October at 8:00 P.M.

Section on Radiology, Southern Medical Association
Secretary, Dr. Andrew F. Giesen, Jr., White-Wilson Clinic, Fort Walton Beach, Fla. 32548. Annual meeting to be announced.

SECTION ON RADIOLOGY, TEXAS MEDICAL ASSOCIATION
Secretary, Dr. George F. Crawford, St. Elizabeth Hospital, Beaumont, Tex. Meets annually with the Texas Medical Association.

SHREVEPORT RADIOLOGICAL CLUB
Secretary, Dr. W. R. Harwell, 608 Travis St., Shreveport, La. Meets monthly on third Wednesday at 7:30 P.M., September to May inclusive.

SOCIETY FOR PEDIATRIC RADIOLOGY
Secretary, Dr. John L. Gwinn, Children's Hospital, 4614 Sunset Blvd., Los Angeles 27, Calif. Annual meeting: Jung Hotel, New Orleans, La., Sept. 30, 1968.

SOCIETY OF NUCLEAR MEDICINE
Secretary, Mr. C. Craig Harris, Oak Ridge National Laboratories, Oak Ridge, Tenn. *Administrator*, Mr. Samuel N. Turiel, 430 N. Michigan Ave., Chicago 11, Ill. Annual meeting Chase-Park Plaza Hotel, St. Louis, Mo., June 27–30 1968.

SOUTH BAY RADIOLOGICAL SOCIETY
Secretary, Dr. Emerson C. Curtis, University Dr., Menlo Park, Calif. 94025. Meets second Wednesday of each month.

SOUTH CAROLINA RADIOLOGICAL SOCIETY
Secretary, Dr. George W. Brunson, 1406 Gregg St., Columbia, S. C. Annual meeting (primarily business) in conjunction with the South Carolina Medical Association meeting in May. Annual fall scientific meeting at time and place designated by the president.

SOUTH DAKOTA RADIOLOGICAL SOCIETY
Secretary, Dr. Donald J. Peik, 1417 S. Minnesota Ave., Sioux Falls, S. Dak. Meets in spring with State Medical Society and in fall.

SOUTHERN CALIFORNIA RADIATION THERAPY SOCIETY
Secretary-Treasurer, Dr. Aaron G. Fingerhut, 1000 W. Carson St., Torrance, Calif. 90502. Mets quarterely.

SOUTHERN RADIOLOGICAL CONFERENCE
Secretary-Treasurer, Dr. Marshall Eskridge, Mobile Infirmary, P.O. Box 4097, Mobile, Ala. 36604. Annual meeting to be announced.

SOUTHWESTERN RADIOLOGICAL SOCIETY
Secretary, John M. McGuire, 904 Chelsea, El Paso, Tex. Meets last Monday of each month at 6:30 P.M. in the Paso del Norte Hotel.

TENNESSEE RADIOLOGICAL SOCIETY
Secretary-Treasurer, Dr. Marion E. Spurgeon, Memorial Hosp., Clarksville, Tenn. Meets annually at the time and place of the Tennessee State Medical Association meeting.

TEXAS RADIOLOGICAL SOCIETY
Secretary, Dr. Herman C. Sehested, 815 Medical Arts Bldg., Fort Worth 2, Tex. Annual meeting to be announced.

TRI-STATE RADIOLOGICAL SOCIETY
Secretary, Dr. John H. Marchand, Jr., Methodist Hospital, Henderson, Ky. Meets third Wednesday of Oct., Jan., March and May, 8:00 P.M., Elks Club in Evansville, Ind.

UNIVERSITY OF MICHIGAN DEPARTMENT OF ROENTGENOLOGY STAFF MEETING
Meets each Monday evening from September to June, at 7:00 P.M. at University Hospital, Ann Arbor Mich.

UPPER PENINSULA RADIOLOGICAL SOCIETY
Secretary, Dr. A. Gonty, Menominee, Mich. Meets quarterly.

UTAH STATE RADIOLOGICAL SOCIETY
Secretary-Treasurer, Dr. Leon M. Neal, St. Benedict's Hospital, 3000 Polk Ave., Ogden, Utah 84403. Meets fourth Wednesday in January, March, May, September and November at Holy Cross Hospital.

VERMONT RADIOLOGICAL SOCIETY
Secretary, Dr. John R. Williams, 160 Allen St., Rutland, Vt.

VIRGINIA RADIOLOGICAL SOCIETY
Secretary-Treasurer, Dr. K. Kenneth Wallace Jr., Norfolk, Va.

WASHINGTON STATE RADIOLOGICAL SOCIETY
Secretary, Dr. Owen Marten, 930 Terry Avenue, Seattle, Wash. Meets quarterly.

WEST VIRGINIA RADIOLOGICAL SOCIETY
Secretary, Dr. George G. Green, Morgantown, W. Va. Meets concurrently with Annual Meeting of West Virginia State Medical Society; other meetings arranged by program committee.

WESTCHESTER COUNTY RADIOLOGICAL SOCIETY
Secretary, Dr. Arnold Gerson, Medical Arts Bldg., Mt. Vernon, N. Y. Meets on third Tuesday of January and October and on two other dates.

WISCONSIN RADIOLOGICAL SOCIETY
Secretary-Treasurer, Harold F. Ibach, 2400 W. Villard Ave., Milwaukee, Wis. 53209. Meets twice a year, May and September.

WYOMING RADIOLOGICAL SOCIETY
Secretary, Dr. J. D. Grant, Memorial Hosp., Sheridan, Wyo. Meets in fall with State Medical Society and in spring on call of President.

CUBA, MEXICO, PUERTO RICO AND CENTRAL AMERICA

ASOCIACIÓN DE RADIÓLOGOS DE CENTRO AMERICA Y PANAMÁ. Comprising: Guatemala, El Salvador, Honduras, Nicaragua, Costa Rica and Panamá.
Secretary-General, Dr. Roberto Calderón, Calle Central Oeste No. 218, Managua, Nicaragua, Central America. Meets annually in a rotating manner in the six countries.

SOCIEDAD DE RADIOLOGÍA DE EL SALVADOR
Secretary, Dr. Julio Astacio, 5a Av. Nte. No. 434, San Salvador, Rep. El Salvador.

SOCIEDAD DE RADIOLOGÍA DE GUATEMALA
Secretary, Dr. Carlos E. Escobar, 9ª. Calle A 0-05, Zona 1, Guatemala.

SOCIEDAD DE RADIOLOGÍA Y FISIOTERAPÍA CUBANA
Secretary, Dr. Miguel A. García Plasencia, Hospital Curie, 29 y F, Vedado, Habana, Cuba Meets monthly at Curie Hospital.

SOCIEDAD COSTARRICENSE DE RADIOLOGIA
Secretary, Dr. James Fernández Carballo, Apartado VIII, San José, Costa Rica.

SOCIEDAD MEXICANA DE RADIOLOGÍA, A.C.
Coahuila No. 35, México 7, D. F.
Secretary-General, Dr. Ramón Ruenes.
Meets first Monday of each month.

ASOCIACIÓN PUERTORRIQUEÑA DE RADIOLOGÍA
Secretary, Dr. R. B. Díaz Bonnet, Suite 504. Professional Bldg., Santurce, Puerto Rico.

SOCIEDAD RADIOLÓGICA PANAMEÑA
Secretary, Dr. L. Arrieta Sánchez, Apartado No. 6323, Panamá, R. de P. Meets monthly in a department of radiology of a local hospital chosen at preceding meeting.

SOCIEDAD RADIOLÓGICA DE PUERTO RICO
Secretary, Dr. Felipe N. de Jesús, Apt. 9387, Santurce, Puerto Rico. Meets second Thursday of each month at 8:00 P.M. at the Puerto Rico Medical Association Bldg. in San Juan.

BRITISH COMMONWEALTH OF NATIONS

ASSOCIATION OF RADIOLOGISTS OF THE PROVINCE OF QUEBEC
Secretary, Dr. R. Robillard, Notre-Dame Hospital, 1560 Sherbrooke St., East, Montreal, Que., Canada. Meets four times a year.

BRITISH INSTITUTE OF RADIOLOGY
Honorary Secretary, Dr. G. H. du Boulay, 32 Welbeck St., London, W. 1, England. Meets monthly from October until May. Annual meeting to be announced.

CANADIAN ASSOCIATION OF PHYSICISTS, DIVISION OF MEDICAL AND BIOLOGICAL PHYSICS.
Honorary Secretary-Treasurer, Paul M. Pfalzner, Dept. of Therapeutic Radiology, University of Western Ontario, London, Ont., Canada. Annual meeting to be announced.

EDMONTON AND DISTRICT RADIOLOGICAL SOCIETY
Secretary, J. D. R. Miller, M.B., University of Alberta Hospital, Edmonton, Alberta, Canada. Meets third Thursday of each month October to May, except December, at various Edmonton Hospitals.

FACULTY OF RADIOLOGISTS
Honorary Secretary, Dr. J. N. Pattinson, 47 Lincoln's Inn Fields, London, W.C.2, England. Annual meeting: London, England, June 21–22, 1968.

FACULTY OF RADIOLOGISTS, ROYAL COLLEGE OF SURGEONS IN IRELAND
Registrar, Dr. H. O'Flanagan, F.R.C.P.I., D.P.H., 123 St. Stephens Green, Dublin 2, Ireland.

SECTION OF RADIOLOGY OF THE ROYAL SOCIETY OF MEDICINE (CONFINED TO MEDICAL MEMBERS)
Meets third Friday each month at 4:45 P.M. at the Royal

Society of Medicine, 1 Wimpole St., London, W. 1, England.

Canadian Association of Radiologists
Honorary Secretary-Treasurer, Dr. Maurice Dufresne, *Associate Honorary Secretary-Treasurer*, Dr. F. Robert MacDonald, 1555 Summerhill Ave., Montreal 25, Que., Canada. Thirty-first Annual Meeting, Chateau Frontenac, Quebec, March 4–9, 1968.

Montreal Radiological Study Club
Secretary, Dr. Leonard Rosenthall, Montreal General Hospital, Montreal, Que., Canada. Meets first Tuesday evening, October to April.

Section of Radiology, Canadian Medical Association
Secretary, Dr. C. M. Jones, Inglis St., Ext. Halifax, N. S.

Société Canadienne-Française de Radiologie
Secretary General, Dr. Jacques Lespérance, 5415 Boul. L'Assomption, Montreal 26, P. Q., Canada. Meets every third Tuesday from October to April. Annual meeting to be announced.

Toronto Radiological Society
Secretary, Dr. George Wortzman, Toronto General Hosp., Toronto 12, Ont., Canada. Meets second Monday of each month, September through May.

College of Radiologists of Australasia
Honorary Secretary, Dr. T. P. Loneragan, c/o British Medical Agency, 135 Macquarie St., Sydney, N.S.W., Australia.

South America

Asociación Argentina de Radiología
Secretary, Dr. Lidio G. Mosca, Avda. Gral. Paz 151, Córdoba, Argentina. Meetings held monthly.

Ateneo de Radiologia
Secretary, Dr. Victor A. Añaños, Instituto de Radiologia, Santa Fe 3100, Rosario, Argentina. Meets monthly on second and fourth Fridays at 7:00 P.M. in the Hospital Nacional de Centenario, Santa Fe 1300, Rosario.

Colégio Brasileiro de Radiologia
Secretary-General, Dr. Miguel Marıc Céntola, Caixa Postal 5984, São Paulo, Brazil.

Sociedad Argentina de Radiologia
Secretary-General, Dr. Osvaldo E. Zerbo, Santa Fe 1171, Buenos Aires. Meetings are held monthly.

Sociedad Boliviana de Radiología
Secretary, Dr. Javier Prada Méndez, Casilla 1182, La Paz, Bolivia. Meets monthly. General assembly once every two years.

Sociedade Brasileira de Radiologia
Secretary, Dr. Armando Rocha Amoédo, Cxa Postal 1532, Rio de Janeiro, Brazil. General Assembly meets every two years in December.

Sociedade Brasileira de Radioterapia
Secretary, Dr. Oscar Rocha von Pfuhl, Av. Brigadeiro Luiz Antonio, 644, São Paulo, Brazil. Meets monthly on second Wednesday at 9:00 P.M. in São Paulo at Av. Brigadeiro Luiz Antonio, 644.

Sociedad Chilena de Radiología
Secretary, Dr. Manuel Concha, Casilla 13426, Santiago, Chile. Meets fourth Friday of each month.

Sociedad Colombiana de Radiologia
Secretary-General, Dr. Armando Uribe, Hospital Militar Central, Apartado aéreo No. 5804, Bogotá, Colombia. Meets last Thursday of each month.

Sociedad Ecuatoriana de Radiología y Fisioterapía
Secretary, Dr. Carlos Palau, Av. Bogotá 206, Guayaquil, Ecuador.

Sociedad Paraguaya de Radiología
Secretary, Dr. Miguel González Addone, 15 de Agosto 322, Asunción, Paraguay.

Sociedad Peruana de Radiologia
Secretary-General, Dra. Ladys del Pino, Instituto de Radiología "Cayetano Heredia" Hospital Arzobispo Loayza, Lima, Perú. Meets monthly except during January, February and March.

Sociedad de Radiologica del Atlantico
Secretary, Dr. Raul Fernandez, Calle 40 #41–110, Baranquilla, Colombia. Society meets monthly at the Instituto de Radiología.

Sociedad de Radiología, Cancerología y Física Médica del Uruguay
Secretary-General, Dr. Ernesto H. Cibils, Av. Agraciada 1464, piso 13, Montevideo, Uruguay.

Sociedade de Radiología de Pernambuco
Secretary, Dr. Manoel Medeiros, Instituto de Radiologia da Faculdade de Medicina da Universidade do Recife, Caixa Postal 505, Pernambuco, Brazil.

Sociedad de Roentgenología y Medicina Nuclear de la Provincia de Córdoba
Secretary-General, Dr. Lucas C. Di Rienzo, Ave. Grl. Paz. 151, Córdoba, Argentina.

Sociedad Venezolana de Radiología
Secretary-General, Dr. Modesto Rivero Conzáles, Apartado No. 9362 Candelaria, Caracas, Venezuela. Meets monthly, third Friday at Colegio Médico del Distrito Federal, Caracas.

Continental Europe

Österreichische Röntgen-Gesellschaft
President, Dr. Konrad Weiss, Mariannengasse 10, Vienna 9, Austria. Meets second Tuesday of each month in Allgemeine Poliklinik. Annual meeting to be announced.

Société Belge de Radiologie
General Secretary, Prof. Simon Masy, Louvain, Belgium. Meets in February, March, May, June, September, October, November and December.

Société Européenne de Radiologie Pédiatrique
Permanent Secretary, Dr. Jaques Sauvegrain, Hôpital des Enfants-Malades, 149, rue de Sèvres, Paris 15e, France. *General Secretary*, Dr. H. Ludin, Department of Roentgenology, Basler Kinderspital, Basel, Switzerland. Annual meeting to be announced.

Société Française d'Electroradiologie Médicale, and its branches: Société du Sud-Ouest, du Littoral Méditerranéen, du Centre et du Lyonnais, du Nord, de l'Ouest, de l'Est, et d'Alger et d'Afrique du Nord. Central Society meets third Monday of each month, except during July, August and September, rue de Seine 12, Paris, France.
Secretary-General, Dr. Ch. Proux, 9 rue Daru Paris 8e, France.

Československá Společnost pro Roentgenologii a Radiologii
Secretary, Dr. Robert Poch, Praha 12, Srobárova 50, Czechoslovakia. Meets monthly except during July, August and September. Annual general meeting.

Deutsche Röntgengesellschaft
Secretary, Professor Dr. med. H. Lossen, Universitäts-Röntgeninstitut, Lagenbeckstr. 1, Mainz, Germany.

Società Italiana di Radiologia Medica e di Medicina Nucleare
Secretary, Dr. Ettore Conte, Ospedale Mauriziano, Torino, Italy. Meets annually.

Nederlandse Vereniging voor Radiologie
Secretary, Dr. C. B. A. J. Puijlaert, Prof. Dondersstraat 73, Tilburg, Netherlands.

Scandinavian Radiological Society
Secretary-General, Dr. C-E. Unnérus, Hagalund-Tapiola, Havsvindsvägen 5 C., Finland. Annual meeting: Copenhagen, Denmark, 1968.

Sociedad Española de Radiología y Electrología Médicas y Medicina Nuclear
Secretary, Juan Gomez Lopez, Villanueva, 11, Madrid 1. Meets every second Friday of each month, Oct. to June, inclusive, in Madrid. Annual general meeting to be announced.

Schweizerische Gesellschaft für Radiologie und Nuklearmedizin (Société Suisse de Radiologie et de Médecine Nucléaire)
Secretary, Dr. Max Hopf, Effingerstrasse 47, Bern, Switzerland.

Asia

Indian Radiological Association
Secretary, Dr. R. F. Sethna, Navsari Building, Hornby Road, Bombay 1, India.

Indonesian Radiological Society
Secretary, Professor Sjahriar Rasad, Taman Tjut Mutiah I Diakarta, Indonesia

Iranian Radiological Society
Secretary, Dr. Issa Yaghmai, P.O. Box No. 14-1151, Teheran, Iran. The Society meets on the second Saturday of each month.

ABSTRACTS OF RADIOLOGICAL LITERATURE

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ROENTGEN DIAGNOSIS

HEAD

OON, C. L. The value of positive contrast ventriculography in pineal and posterior fossa tumours. *Singapore M. J.*, June, 1967, *8*, 111–122. (From: Department of Radiodiagnosis, General Hospital, Singapore, Singapore.)

Positive contrast ventriculography has proven a valuable procedure in localization and diagnosis of masses in the pineal and posterior fossa regions, while anatomic variation limits the usefulness of vertebral arteriography, the hazard of herniation limits pneumoencephalography, and isotope localization is of only moderate accuracy in the posterior fossa. Because of technical difficulty in manipulation and visualization of small volumes of air in ventriculography, many workers have turned to myodil (pantopaque) ventriculography. The potential hazard of iodinated oil in the ventricular and subarachnoid space remains under discussion, with recent experiments suggesting that it may not be irritating unless blood is present.

At General Hospital in Singapore, air is employed first and if the study is inconclusive, this is followed by positive contrast medium ventriculography. Fluoroscopic control and filming are no longer employed here, the manipulation and filming being as follows: 1–2 cc. are instilled into the lateral ventricle with the patient prone with head flexed. The patient is then brought backwards until he is kneeling on the table with trunk and head extended (termed by author the "Al Jolson attitude"). Slight contralateral head tilt during the extension maneuver facilitates flow of the medium from the frontal horn through the foramen of Monro to the posterior third ventricle. With head still hyperextended, the patient is placed supine, and when slight head flexion results in filling of the aqueduct and fourth ventricle, roentgenograms are obtained in frontal, Towne and cross-table lateral projections.

In analyzing the roentgenograms for evidence of displacement of normal structures, the author employs 3 landmarks. The standard Swedish and Twining points are employed for the localization of the aqueduct and fourth ventricle, respectively. The "Singapore method" of pineal localization is introduced. A line is drawn from the tuberculum sellae to the anterior lip of the foramen magnum. A perpendicular arm is erected 1 cm. from the tuberculum. The expected position of the pineal gland is given by a point 5 cm. on this arm.

The author reports a group of representative cases, illustrating the appearance of typical lesions of the posterior fossa and posterior third ventricle.—*Rosalind H. Troupin, M.D.*

NECK AND CHEST

FARRELL, V. J., and HAWKINS, T. DESMOND. Glomus jugulare tumours with special reference to their radiological features. *Brit. J. Surg.*, Sept., 1967, *54*, 789–795. (Address: V. J. Farrell, 40 Eighth Avenue, Parktown North, Johannesburg, South Africa.)

Glomus jugulare tumors are benign, locally invasive tumors originating from the chemoreceptor system. The first involvement is commonly in the middle ear, from which spread may occur in any direction, with variation of clinical presentation depending upon which cranial nerves are affected and the direction of spread. The internal jugular vein may be affected by compression or intraluminal extension. Over 300 cases have been reported in the literature. Often the preoperative diagnosis is incomplete.

The authors describe 2 cases. Both were worked up roentgenologically with plain skull roentgenograms, tomograms of the petrous bones, carotid and vertebral angiography, jugular phlebography, and contrast venticulography. Bone involvement was precisely localized from the plain roentgenograms and tomograms. The vascular supply of both tumors was from external carotid and vertebral-basilar arteries. Involvement of both jugular veins was demonstrated by phlebography, and displacement of posterior fossa structures confirmed by ventriculography. Both cases were inoperable as judged at surgery, and both had brisk hemorrhage following limited biopsy.

If these cases are adequately studied, surgery can often be avoided, and a firm diagnosis can be established without resort to biopsy which is not without danger.—*Mark D. Reiss, M.D.*

SAKULA, ALEX. Mushroom-worker's lung. *Brit. M. J.*, Sept. 16, 1967, *2*, 708–710. (Address: Consultant Physician, Redhill General Hospital, Surrey, England.)

Four cases of mushroom worker's lung in Sussex, England, are described who developed respiratory disorders thought to be related directly to their occupation. Some hours after exposure the patients developed fever, headache, vomiting and myalgia, subsequently giving way to symptoms of acute respiratory distress, with cough, chest pain and dyspnea.

Roentgenologic findings consisted of a diffuse miliary type of parenchymal mottling, often with associated hilar prominence. These abnormalities, as well as the clinical manifestations, cleared following removal from the environment.

Mushrooms are commercially grown on a compost

mixture which has gone through a steam pasteurization process designed to kill organisms which would interfere with mushroom growth. The process, however, is conducive to growth of certain thermophilic mold contaminants. During the hand planting (spawning) of mushroom mycelia in the compost, a great deal of mold-containing dust is liberated.

The clinical and roentgenologic features bear a close resemblance to those seen with "farmer's lung"—hypersensitivity reaction to an antigen present in the dust of mouldy hay. Two of the 4 patients presented here had demonstrable precipitin antibodies to thermophilic fungi.

The author feels that mushroom worker's lung is a variant of farmer's lung and does not represent hypersensitivity to the mushrooms themselves.—*Rosalind H. Troupin, M.D.*

Schneider, Rea M., Nevius, Donald B., and Brown, Harold Z. Desquamative interstitial pneumonia in a four-year-old child. *New England J. Med.*, Nov. 16, 1967, *277*, 1056–1058. (From: Cedars of Lebanon Division, Cedars-Sinai Medical Center, Los Angeles, Calif.)

Previous reports of desquamative interstitial pneumonia have been in adults.

This case is of a 4 year old girl with cough, tachypnea, and weight loss for 2 weeks. A recent nonspecific upper respiratory tract infection was noted in the family. Physical examination was negative except for rapid respiration. Chest roentgenograms showed bilateral hilar and paratracheal lymphadenopathy, and a vague infiltrate at the right base. Extensive study failed to reveal bacterial or tuberculous etiology, and several viral studies were negative. While running a low grade fever she was discharged on tetracycline, only to be readmitted in a month with progressive deterioration of her condition, cyanosis, and diffuse increased densities throughout both lung fields. An open-lung biopsy revealed proliferation of the alveolar lining cells and masses of similar cells in the alveolar lumina—typical microscopic findings of the disease first described by Liebow (*Am. J. Med.*, 1965, *39*, 369–404), who concurred in the diagnosis of this case. The clinical condition markedly improved following corticosteroid therapy, which is true of the other cases reported. The sole difference between this case and other adult cases is the presence of lymphadenopathy, which has not heretofore been reported.

This case illustrates the value of open-lung biopsy in diffuse pulmonary disease.—*Mark D. Reiss, M.D.*

Doering, P., and Lorenz, B. The demonstration of pulmonary embolism with ^{131}I-albumin particles. *German Med. Monthly*, June, 1967, *12*, 253–258. (From: The Department of Medicine, Hospital of the Compassionate Brothers, Regensburg, Germany.)

Eleven patients with the final clinical diagnosis of pulmonary embolism were scintiscanned using radioactive albumin particles. In 8 of these patients the scan was abnormal and the abnormality usually appeared as an extensive filling defect. Six of the 11 cases also had an abnormal chest roentgenogram, including the 3 with a normal scintiscan.

A dose of 200–300 μc of the material was given intravenously with the patient recumbent, taking 30 seconds for the injection to allow good admixture with the blood.

The authors confirm the observation made by other investigators that the scan may remain abnormal for a long period of time after clinical and roentgenographic recovery.

They conclude that, because of its ability to provide early confirmation of pulmonary embolism in a large proportion of cases, lung scanning is a valuable aid to diagnosis. It is easily performed with no allergic or hemodynamic reactions and offers a very low radiation exposure.—*Everett H. Johnston, M.D.*

Van Vaerenbergh, P. M., and Schelstraete, K. La scintigraphie pulmonaire vasculaire. (Pulmonary vascular scintigraphy.) *J. belge de radiol.*, 1967, *50*, 273–287. (From: Clinique de Radiothérapie et de Médicine Nucléaire, Université de Gand, Belgium.)

The lung scan serves as a visual demonstration of the capillary flow of blood coming from the pulmonary artery. Zones of ischemia become manifest as "cold" or inactive areas. Thus, in addition to a study of pathologic anatomy, a lung scanning presents an excellent method of measuring pulmonary blood flow and of demonstrating regional alterations of this flow.

The introduction of macroaggregate albumin tagged with I^{131} and, more recently, with Tc^{99m}, has started a new era of progress in this field.

The thyroid gland is blocked with Lugol's solution when I^{131} is used, and with perchlorate when Tc^{99m} is used.

A dose of 200–250 μc of MAA tagged with either I^{131} or Tc^{99m} is slowly injected intravenously, with the patient in the supine position. This position affords a more homogeneous distribution in the lung. Scanning is started immediately, using a Picker Magnascanner with a 3 or 5 inch crystal, at a speed of 60 cm./min. The procedure is simple, free of side reactions and is well tolerated by the patient.

The biologic half life of these isotopes is approximately 6 hours. With a dose of 200 μc I^{131}MAA, the lung radiation dose is 1.3 rads and is 100 times less when the same dose of Tc^{99m}MAA is used.

Scannings are performed in the anteroposterior

supine position. In cardiomegaly, the retrocardiac portion of the lung is best examined with the patient in the prone position. This position, however, is poorly tolerated by the dyspneic patient.

While pulmonary angiography may give more detailed information, lung scanning is a simple and safe procedure and may be repeated, as needed, especially in evaluating the progress and evolution of pulmonary infarction and embolism.

A total of 127 lung scannings were performed on 108 patients, of which 9 were normal. The others included pulmonary embolism and infarction, primary and metastatic malignant disease, abscess, bullous emphysema, atelectasis, pleural disease, tuberculosis, cysts and subphrenic abscess.

The extent of pulmonary involvement and the diminution of regional blood flow were greater than would be anticipated by the appearance of the routine chest roentgenograms.

One table, and reproductions of scans and roentgenograms of 11 illustrative cases accompany this article.—*William H. Shehadi, M.D.*

MACLEAN, LLOYD D., SHIBATA, HENRY R., MCLEAN, A. P. H., SKINNER, G. BERNARD, and GUTELIUS, JOHN R. Pulmonary embolism: the value of bedside scanning, angiography and pulmonary embolectomy. *Canad. M. A. J.*, Oct. 17, 1967, *97*, 991–1000. (Address: L. D. MacLean, Surgeon-in-chief, Royal Victoria Hospital, 687 Pine Avenue W., Montreal 2, Quebec, Canada.)

The authors report on their experience in scintillation scanning of 104 patients suspected of pulmonary embolism using I^{131} macroaggregates of serum albumin. These scans were obtained at the bedside and were negative in 51 patients. In 8 of these patients who died, pulmonary embolism was not found at autopsy. All of the 53 patients with positive scans received heparin. In 2 patients with hypotension and a mean right venticular pressure exceeding 22 mm. of mercury, embolectomy and inferior vena cava plication were performed successfully. If the mean right ventricular pressure was less than 22. mm of mercury, only inferior vena cava plication was done. Patients were also treated with isoproterenol, heparin, bed rest and oxygen. Eight of the patients treated medically died, 5 from unrelated causes, suggesting the possibility of false positive scans. Three patients who were awaiting angiography and manometry after a positive scan all died of pulmonary embolism.

During the period of this study 24 patients who did not have a bedside scan died of pulmonary embolism. In many of the 24 the correct diagnosis was suspected clinically but treatment was begun in only 3 indicating the value of scanning in the diagnosis of pulmonary emboli.—*Merle K. Loken, Ph.D., M.D.*

BEFELER, BENJAMIN, MACLEOD, CATHEL A., BAUM, GERALD L., and SCHWARTZ, HAROLD. Idiopathic dilatation of the pulmonary artery. *Am. J. M. Sc.*, Nov., 1967, *254*, 667–674. (From: Cardiology Section, Medical Service, Veterans Administration Hospital, Western Reserve University, Cleveland, Ohio.)

The authors present 2 case reports and discuss the entity of idiopathic dilatation of the pulmonary artery. They point out that this is a rare lesion and that the diagnosis must be made by exclusion.

In both their cases there was a full medical workup including cardiac catheterization and angiography.

They raise the question as to whether or not this condition may be associated with some congenital abnormality of the wall of pulmonary artery similar to that found in the aorta in Marfan's syndrome.

Good criteria for the diagnosis are laid down in the text, but there will still be some who find the diagnosis of idiopathic dilatation of the pulmonary artery hard to accept, especially without a fuller discussion of the mobility and normality of the pulmonary valve on cineangiography.—*Roger Pyle, M.D.*

MOES, C. A. F., GOLDMAN, B. S., and MUSTARD, W. T. Anomalous pulmonary venous drainage from the left lung into a left vertical vein. *J. Canad. A. Radiologists*, Sept., 1967, *18*, 377–381. (From: Departments of Radiology and Surgery, The Hospital for Sick Children, Toronto, Ontario, Canada.)

The authors describe 2 cases of anomalous pulmonary venous drainage from the left lung into a left vertical vein. Partial anomalous insertion of pulmonary veins may occur in various structures. Those on the right often insert into the superior vena cava or right atrium, or both. They may also join the inferior vena cava or the azygos vein. The condition is less common on the left. They may insert into the innominate vein, a left vertical vein or the coronary sinus, and rarely into the inferior vena cava or the right atrium. Cases have been reported in which the left pulmonary veins drained into a persistent left superior vena cava which joined the coronary sinus. Here the 2 superior venae cavae were joined by a left innominate vein.

The vein connecting the left pulmonary veins and the left innominate vein is a persistent left superior vena cava only if there is a connection between this vein and the heart. This becomes important because the persistent left superior vena cava represents the left anterior cardinal vein whose proximal end becomes the coronary sinus. When no connection with the heart can be demonstrated, the vein is

designated as the "vertical anomalous pulmonary vein." Many suggest that the channel from the vein to the heart may have been obliterated during fetal development and that both these veins are the same.

The entity is similar to an atrial septal defect clinically, electrocardiographically and hemodynamically. Cyanosis is not a feature and fatigue and exertional dyspnea usually occur only in adulthood. There is a left to right shunt diastolic overloading, right axis deviation and right ventricular hypertrophy. An associated atrial septal defect is common.

The chest roentgenogram shows a widening of the left superior mediastinum from the main pulmonary artery to the aorta. It also reflects the degree of left to right shunt. Hypoplasia of the lung and hemithorax on the side of involvement with shift of the mediastinum to the affected side has been seen with right-sided involvement.

Selective angiocardiography demonstrated the vertical vein with near simultaneous opacification of both atria. The atrial septal defect was not demonstrated.

Surgical correction consists of closing the atrial septal defect if present and anastomosing the vertical vein to the left atrium while ligating the vertical vein proximal to its insertion into the left innominate vein.—*James R. Stevenson, Major, MC*

Abdomen

Williams, D. Innes, and Burkholder, George V. The prune belly syndrome. *J. Urol.*, Aug., 1967, *98*, 244–251. (From: The Hospital for Sick Children, Great Ormond Street, London, England.)

The characteristic features of this syndrome are congenital defects or absence of the abdominal muscles particularly from the lower and medial region of the abdominal wall, cryptorchism, dysplasia of the entire urinary tract including the kidneys, ureters and bladder usually with marked hydronephrosis, defects in the lower extremities, heart, or gastrointestinal tract. The disease is more common in boys, with an incidence of 134 males to 6 females of 140 cases reported in the literature. There is a strong suggestion that the condition is due to a sex-linked recessive trait; but in those cases which have been studied up to the present time, no chromosomal abnormalities have been detected.

On physical examination of the patient, the skin over the abdominal wall is wrinkled somewhat as a wizened prune, and the abdominal muscles do not respond to electrical stimulation.

The urinary tract disease is extremely important and many of these patients do not survive birth or infancy because of advanced urinary tract dysplasia. The kidneys are poorly developed and cystic changes may be present. The ureters may be tremendously dilated with increase in fibrous tissue and diminution in musculature. The bladder is characteristically capacious and may hold as much as 600 to 1,300 ml. Trabeculation of the bladder is not usually present, but reflux during cystography is common. The ganglion cells of the bladder and lower urinary tract have not been found to be abnormal. A patent urachus may be present in some instances. The characteristic picture of the bladder base is a wide tapering of the posterior portion to a point near the membranous region of the urethra. In some instances, a tubular diverticulum is seen and this may be utricular in origin. In some of these patients there is a mechanical obstruction associated with congenital valves of the urethra, but this is not an important part of the syndrome. The pressure flow studies of the urinary bladder indicate that the changes in the urinary tract of patients with absent abdominal muscles do not occur as the result of increased urethral resistance or obstruction, although this finding may be present in a minority of instances. Maximum micturating pressure and urine flow, the best measures of detrusor action, have been shown to be within normal range.

This article suggests that in male patients with absent abdominal muscles the entire urinary tract is developmentally imperfect. If there is a mechanical obstruction, it will be found in the lower part of the posterior urethra, but the majority of patients do not show this lesion. The more severe cases suffer from renal failure due to primary dysplasia. In these patients the abnormalities of the urinary tract and other systems will frequently result in stillbirth or renal failure during the early months of postnatal life. Those who may survive are subject to urinary tract infection and the control of this infection appears to be the most helpful aspect of their treatment.—*George W. Chamberlin, M.D.*

Bourne, Charles W., and Cerny, Joseph C. Congenital absence of abdominal muscles: report of six cases. *J. Urol.*, Aug., 1967, *98*, 252–259. (From: The Section of Urology, Department of Surgery, University of Michigan Medical Center, Ann Arbor, Mich.)

The syndrome associated with absence of the abdominal muscles was first described in 1839 and at the present time more than 100 cases have been documented. The patients are usually of the male sex and the syndrome is associated with anomalies of the muscles of the abdominal wall, dysplasia of the kidneys, ureters and bladder, undescended testicles, skeletal anomalies such as talipes equinovarus, congenital dislocation of the hips, and anomalies of the intestinal tract and heart.

In this article 6 case reports are presented showing the clinical and pathologic features of the urinary tract lesions. The imperfect muscularization or

dysplasia of the abdominal skeletal muscles and the smooth muscle of the urinary conduits produce the clinical findings of a wrinkled protuberant abdominal skin with dilatation of the bladder and upper urinary tracts. In some of the reported cases, a primary obstructive lesion in the lower urinary tract may have contributed to the hydronephrosis, hydroureter and overdistention of the bladder. Definite posterior urethral valves were diagnosed in 5 cases in a series of 90 patients with this syndrome. The most common abnormality was a median bar or a stenosis of the vesical neck, but phimosis or valves of the urethra also have been found.

Whenever possible urinary tract infection should be treated and any obstructive lesion should be removed.—*George W. Chamberlin, M.D.*

WILSON, T. S., and COSTOPOULOS, L. B. The diagnosis and treatment of pancreatic pseudocysts. *Canad. M. A. J.*, Nov. 4, 1967, *97*, 1117–1128. (Address: T. S. Wilson, M.D., Department of Surgery, University Hospital, Edmonton, Alberta, Canada.)

A history of pancreatitis or blunt trauma to the abdomen should alert the attending physician to the possibility of a pancreatic pseudocyst. The patient may recover from the original attack of pancreatitis, and then gradually, over a period of 2, 3 or 4 weeks, a mass may become palpable in the epigastrium. It is usually smooth and round, rather indistinct and only slightly tender. Following trauma, the mass often appears more quickly. Persistent pain and ileus may develop and the serum and urine amylase may remain elevated (2 to 3 times of normal).

Sixteen patients are reported and in one-half of these a diagnosis of pseudocyst was first suggested by the radiologist.

A pseudocyst, or false cyst, is defined as an abnormal sac containing fluid, the lining of which is devoid of epithelium.

A roentgenogram of the abdomen may show a nonspecific, soft-tissue mass, usually in the left upper quadrant, which on rare occasions contains calcification. The adjacent organs may be displaced. Upper gastrointestinal series may reveal degrees of extrinsic pressure upon the stomach, duodenum and jejunum, depending on the origin of the cyst. Typically, a cyst arising from the head of the pancreas produces widening of the duodenal loop and upward displacement of the greater curvature of the stomach. The mucosal folds of the stomach and duodenum may be strecthed but are intact. Cysts arising from the tail of the pancreas may displace the stomach anteriorly and medially, and the proximal jejunum and the splenic flexure caudally. A cyst of the body of the pancreas usually displaces the stomach anteriorly and superiorly, and in some instances laterally. Intravenous cholangiography or percutaneous transhepatic cholangiography may reveal lateral displacement of the common bile duct and obstruction by a pseudocyst of the head of the pancreas. Roentgenograms of the chest may show an elevated left diaphragm and occasionally an effusion in the left pleural cavity.

Pseudocysts rarely resolve spontaneously and if left alone they may become infected, may hemorrhage, develop a fistula, or produce duodenal or common bile duct obstructions and thus jaundice. The most important complication is spontaneous rupture into the general abdominal cavity with peritonitis. Occasionally a cyst may perforate into the bowel (and thus may cure itself), into the mediastinum and lung, retroperitoneally and even externally. If the patient's condition permits, pseudocysts should be operated upon when first diagnosed. Fluid and electrolytes should be replaced before operation. Commonly the cyst is behind the stomach or points through the gastrohepatic or gastrocolic omentum, or through the undersurface of the transverse mesocolon.

In the past 10 years an increasing number of pseudocysts have been drained internally into the stomach. Since the majority lie behind the stomach and are fused with the posterior gastric wall, the simplest access to the cyst is to open the interior wall of the stomach and make a circular 2 to 3 cm. opening through the posterior gastric wall into the cyst. To keep the opening patent, the cyst wall is sutured to the opening in the posterior wall of the stomach. The method is safe and easy to perform and the results on the whole have been excellent. Not all pseudocysts can be drained by cystogastrostomy. Those in peculiar positions are best treated by simple tube drainage, using a No. 16 soft rubber mushroom catheter. A small cyst in the tail of the pancreas can be excised by distal pancreatectomy.

Seven of the 16 patients were treated by tube drainage and 8 by cystograstrostomy. The cyst recurred in 3 patients treated by tube drainage and a second operation was necessary. There have been no recurrences except in those treated by tube drainage. None died and the final result in each case was good.—*David Morse, M.D.*

BURKINSHAW, J. H., O'BRIEN, D., and PENDOWER, J. E. H. Cushing's syndrome associated with an islet-cell tumour of the pancreas in a boy aged 2 years. *Arch. Dis. Childhood*, Oct., 1967, *42*, 525–531. (From: Mayday Hospital, Croydon, London, England.)

The subject of this case report was first seen at the age of 2 years and 3 months because of sudden excessive weight gain. He had been healthy and free of symptoms until 6 weeks before, when he suddenly developed ravenous appetite. He became very fat and his face had become very red. He gained 7½ lb.

during this interval. There were no other symptoms, and he was lively and cheerful, with no polydipsia or polyuria.

On physical examination he had a red moonface, and there was faint brownish pigmentation of the entire skin with no pigment inside the mouth. The genitalia were not enlarged and there was no hirsutism. Two blood pressure readings of 110 mm. Hg were recorded by the flush and palpation methods using a 10 cm. cuff. A firm, nontender rounded mass about the size of an orange could be felt in the left hypochondrium. Grossly elevated plasma cortisol and urinary oxogenic steroid excretions were observed.

Intramuscular pyelography demonstrated a large soft tissue mass below and lateral and possibly anterior to the kidney, and was displaced by the splenic flexure downward.

At operation a large retroperitoneal tumor was found in the tail of the pancreas. Distal hemipancreatectomy and splenectomy were performed. The left adrenal gland was seen to be the size of a forefinger nail and thin. It was thought to be normal in size. The right adrenal gland was also thought to be normal.

The specimen weighed 21 grams. Sections showed a tumor composed of small polygonal or spherical cells which in places closely resembled the cells of the islets of Langerhans in the attached normal part of the pancreas.

The patient has been symptom-free for 1 year following the operation.

The importance of confirming the diagnosis of Cushing's syndrome by finding evidence of increased adrenal cortical activity derived from tests of cortical steroid metabolism is stressed. Ross, Marshall-Jones and Friedman have found that the most useful test is the measurement of the amount of free cortisol in the urine, and the next most reliable is the dexamethasone suppression test, adrenal overactivity being strongly suggested by failure of this substance to suppress the urinary excretion of 17-ketogenic steroids below 3 milligrams per day.

Cushing's syndrome in its modern connotation associated with nonadrenal tumors is well documented. By far the commonest primary tumor is an oat cell carcinoma of the lung, but tumors in many other sites have been incriminated, including islet cell tumors of the pancreas. It has been shown that these nonadrenal tumors do in fact secrete a substance biologically and immunologically similar to ACTH which suppresses the normal ACTH producing mechanisms of the pituitary. It seems that the production of this ACTH-like substance is autonomous, because it is not suppressed by large doses of dexamethasone. There appears to be no constant relation between size and functional activity of the adrenal glands. The explanation for this postulates the existence of two types of corticotrophin, one that maintains the weight of the adrenal glands and the other that releases the steroids. This may be the explanation for the absence of enlargement of the adrenal glands in this patient.—*David Morse, M.D.*

Genitourinary System

Cerny, Joseph C., Kendall, A. Richard, and Nesbit, Reed M. Subcutaneous pyelography in infants: a reappraisal. *J. Urol.*, Sept., 1967, *98*, 405–409. (From: The Section of Urology, Department of Surgery, University of Michigan Medical Center, Ann Arbor, Mich.)

This is a brief summary of the authors' experience in the selection of the least irritating contrast medium for subcutaneous injection based upon animal injection and histologic examination. In addition, the authors present their experience with subcutaneous injection of pyelographic media in 100 infants.

For the experimental studies large white rabbits were anesthetized and after proper preparation injected subcutaneously with 20 cc. of 50 per cent urokon, hypaque, miokon, renografin, and conray. Sections of skin and subcutaneous tissue were studied histologically at intervals of 12 hours and 1, 2, 3, 5, 8, and 10 days following the injection. The degree of inflammatory reaction was graded. The contrast medium which was found to be the least irritating in rabbits was hypaque.

This substance was used in the following clinical trials of 100 infants. Thirty cc. of 50 per cent hypaque was diluted to a volume of 100 cc. with 5 per cent dextrose and water. Under sterile precautions this was injected through a 21 gauge needle in the subcutaneous tissues over the scapular and axillary area with 50 cc. quanta injected over each side. This produced considerable ballooning of the overlying skin which returned to normal after a period of 1 hour.

Satisfactory pyelograms were obtained in 98 infants. The majority of pyelograms were interpreted as normal, but Wilms' tumor was found in 1 patient and varying degrees of upper urinary tract dilatation were seen in several patients. Generally, the best visualization was obtained 30, 45, or 60 minutes after injection. Of 2 patients with poor quality subcutaneous pyelograms, one infant had an elevated blood urea nitrogen of 76 mg. per cent, and the other infant was anemic with a hemoglobin of 6 grams per cent. No allergic reactions were encountered.

The authors conclude that the subcutaneous injection of hypaque in infants can be a safe and satisfactory procedure for pyelography.

Two tables and 6 figures illustrate the authors' findings.—*George W. Chamberlin, M.D.*

FAURE, CLÉMENT. (Paris, France.) Les maladies kystiques des reins chez l'enfant. (Renal cystic disease of children.) *J. Canad. A. Radiologists*, Sept., 1967, *18*, 356–370.

By definition, a renal cyst is a well defined (closed) pocket, lined with epithelium, filled with fluid, located in the renal parenchyma at the expense of renal tissue, and independent of the collecting system. This excludes microcysts in the parenchyma due to chronic nephritis, hydrocalyx, tubercular cavities, juxtacalyceal cysts associated with chronic pyelonephritis and ulcerating carcinoma. Excluded also are cysts due to parasitic disease.

In a study of cysts of the kidney, noteworthy is the age at which the cyst appears, its histopathology, the extent of involvement of kidney substance, cortical or medullary location, the genetic or hereditary factors, the radiologic appearance, and whether the cyst is solitary or multiple, unilateral or bilateral. The following types are discussed: parapelvic; solitary; multiple; multicystic renal displasia; precalyceal tubular ectasia (this falls in a special category occurring in the young adult, rarely in children); hereditary renal polycystic disease as opposed to bilateral polycystic kidney of the adult (manifest at age of 40–50 years); and juvenile polycystic hepatorenal disease (a rare hereditary and possibly familial disease, in which marked enlargement of the liver, rather than kidney, is the dominant finding).

The author appeals for more widespread case reporting, uniformity of classification and nomenclature, with evaluation of the clinical, radiologic, histopathologic and genetic factors.

Twelve reproductions of photographs of anatomic specimens and roentgenograms accompany this article.—*William H. Shehadi, M.D.*

MAGED, ALY. Renal chyluria. *Brit. J. Urol.*, Oct., 1967, *39*, 555–559. (From: The Department of Urology, Faculty of Medicine, Ein Shams University, Egypt, U.A.R.)

Twelve cases of unilateral renal chyluria are reviewed in this article from Egypt. Chyluria, or chyle in the urine, is due to a communication between the intestinal lymphatics and the urinary tract. It may occur at any level in the urinary tract, but a renal site is most common and it is usually unilateral. The common form, parasitic chyluria, is due to the late effect of the filarial worm *Wuchereria bancrofti* infestation, although other co-existing parasites have been identified. Nonparasitic chyluria is rare.

Except when excessive loss of fats results in general malnutrition, the usual case offers no threat to the general health. The milky urine observed by the patient may be constant in appearance or intermittent. Urinalysis reveals a high fat content and red and white blood corpuscles as well as albumin, globulin and fibrinogen in the urine. The fibrinogen loss sometimes results in clot formation and subsequent attacks of renal colic and obstruction.

Eleven of the 12 cases presented were felt to be due to filarial infection, although no microfilariae were detected. Filariasis is endemic in Egypt and microscopic confirmation is often not considered. The other single case was due to involvement of abdominal and pelvic lymphatics by metastatic prostatic carcinoma.

The cases were evenly divided among the two sexes and the patients ranged in age from 27 to 59 years. Examination of the urinary tract revealed bilharzial calcification in the bladder wall in 3 cases. Intravenous pyelographic studies were normal. Retrograde pyelography performed in 11 cases revealed normal appearance in 8 cases, a filling defect in the upper pole calyces in 1 case and opacified lymphatic channels arising from the pyelocalyceal system in 2 cases.

Treatment, consisting of fatty dietary restrictions in 1 case, instillation of 2 per cent silver nitrate solution into the renal pelvis in 2 cases, and of 15 per cent sodium iodide in 1 case, was unsuccessful. Renal lymphangiectomy in 5 cases resulted in reported cure without recurrence. Other surgical treatments included decapsulation, retroperitoneal lymphatic to spermatic vein shunt, and nephrectomy when the patient's general condition was threatened. Lymphangiectomy although successful, theoretically deprives the kidney of its lymphatics and therefore its safety valve, if lower tract obstruction should develop.—*John T. Underberg, M.D.*

DAUTREBANDE, JACQUES, DUCKETT, GUY, and ROY, PAUL. Arteriography in renal tuberculosis. *J. Canad. A. Radiologists*, Sept., 1967, *18*, 382–388. (Address: Guy Duckett, M.D., Hôpital Jean-Talon, Montreal, Quebec, Canada.)

The best method of angiographic evaluation of renal tuberculosis is by the selective renal arteriographic procedure. Early in the disease only small arterial strictures, dilatations and displacements are seen and these are nonspecific. Later when one or more calyceal groups are not visualized due to cicatricial stricture between calyces and renal pelvis, angiography is more valuable than urography in establishing a diagnosis. When the disease is advanced, angiography is confirmatory and often with nonvisualization is the only method of demonstrating the abnormalities. It is also particularly valuable in demonstrating parenchymal defects.

The authors studied 10 cases and found a triad of signs on the angiogram which suggests tuberculosis: (1) Signs of moderate hydronephrosis; (2) peripheral signs—abnormalities of the small vessels accompanied by irregularities or thinning of the

cortex; and (3) a small kidney. Of the 10 cases, 6 were proven and divided into two groups (one group in which one kidney was diseased entirely and another group in which the lesions were localized to one pole). In the arteriographic phase the primary and secondary arteries were diverging and elongated as in hydronephrosis, the more distal arteries being irregular, sparse and rigid; the peripheral arteries were moth-eaten and often have disappeared. In the nephrographic phase there were significant differences in the thickness of the cortex as in pyelonephritis. If the thinning was uniform as in hydronephrosis, the kidney was never large but was normal or small in size.

Renal tuberculosis with ureteral involvement is the condition most likely to cause the triad. Other possibilities such as bacterial pyonephrosis, retroperitoneal fibrosis, and ureteral tumor, should not be overlooked. The authors had 2 cases of low ureteral carcinoma showing signs of hydronephrosis and a small kidney but no evidence or pyelonephritis.

It is felt that the signs are due to a chronic process causing slow and progressive destruction of the renal parenchyma.—*James R. Stevenson, Major, MC*

Hamilton, R. W., and Swann, J. C. Corpus cavernosography in Peyronie's disease. *Brit. J. Urol.*, Aug., 1967, *39*, 409–414. (From: The Department of Urology and Radiodiagnosis, The London Hospital, E.1, London, England.)

Six patients with Peyronie's disease were studied by the roentgenographic technique of corpus cavernosography. This consisted of injection of a radiopaque medium (60 per cent urografin) into the corpora. The technique gives a method of objectively delineating the extent of the fibrotic process.

Five patients of the group received combined hydrocortisone and hyalase injections without any evidence of improvement.—*Frank J. Kulbaski, M.D.*

Brown, Jordan, S., Dubin, Lawrence, Becker, Melvin, and Hotchkiss, Robert S. Venography in the subfertile man with varicocele. *J. Urol.*, Sept., 1967, *98*, 388–392. (From: The New York University Medical Center, New York, N.Y.)

Internal spermatic venography was performed at the time of varicocelectomy in 35 consecutive subfertile men. Twenty-seven of these had a left varicocele, 4 had bilateral varicoceles and 4 did not have a definitive lesion but did have seminal abnormality similar to that seen in patients with varicocele.

While the patient was on the operating table prior to doing a high complete ligation of the internal spermatic venous system above the internal inguinal ring, a No. 16 catheter was introduced into the exposed internal spermatic vein in the direction of the renal vein and subsequently toward the testis. Radiopaque material was then instilled at a rate of 4 to 6 cc. per minute under low pressure with the patient's head elevated at a 45° angle. Roentgenograms were obtained during the injection of the radiopaque material into the renal vein and also into the spermatic vein.

The venograms were analyzed according to the following criteria: (1) appearance of the renal vein; (2) caliber of the internal spermatic vein; (3) existence of valvular deformities in the internal spermatic vein; (4) angle at which the internal spermatic vein joins the renal vein; (5) presence of retrograde flow of radiopaque material down the internal spermatic vein; (6) appearance of cross collateral circulation between the 2 testes; and (7) termination of the right internal spermatic vein in patients with right varicoceles.

The procedure was successful in 26 patients, partly successful in 7 patients and failed in 2 patients.

In the 4 subfertile men without varicoceles venography disclosed a left internal spermatic vein of normal caliber with a right angle termination into the renal vein and cut-off of radiopaque material prior to the junction of the renal vein with the inferior vena cava in all studies. In 3 of the 4, definite defects suggesting valves could be demonstrated in the course of the internal spermatic vein and there was cross collateral venous circulation.

Of the 24 subfertile men with left varicocele, 20 showed a dilated internal spermatic vein with valve-like appearances in only 4. Retrograde flow of the opaque material was noted in 11 and cross collateral circulation was present in 9. Thirteen showed dilated renal veins and 17 showed termination of the renal vein prior to the junction with the inferior vena cava.

In the subfertile men with bilateral varicoceles, valves were absent in all but one of the right internal spermatic veins and in all of the left internal spermatic veins. Cross collateral circulation could be demonstrated in all cases. Retrograde flow of opaque material occurred in 2 patients and the right internal spermatic vein could be identified entering the right renal vein instead of the inferior vena cava in 2 instances.

Venographic studies of this type indicate that varicocele is not a unilateral circulatory disturbance but is a potentially bilateral abnormality.

The characteristic seminal abnormality in varicocele consists of an abnormal morphology with abundance of immature forms, and impairment in motility and to a lesser degree of depression in the sperm count. The most consistent and dramatic

improvement postoperatively has been noted in sperm motility and this is probably the most important parameter of fertility potential. The authors suspect that endocrine or toxic metabolic substances passing in the retrogressing blood from either the left kidney or adrenal gland into the circulation of both testes at abnormally high concentrations may be spermatocidal and result in impaired spermatogenesis.

Six composite illustrations are included in this article.—*George W. Chamberlin, M.D.*

Nervous System

Onji, Yutaka, Akiyama, Hiroyuki Shimomura, Yutaka, Ono, Keiro, Hukuda, Sinsuke, and Mizuno, Syotaro. Posterior paravertebral ossification causing cervical myelopathy: a report of eighteen cases. *J. Bone & Joint Surg.*, Oct., 1967, *49A*, 1314–1328. (Address: Y. Onji, Nara Medical College Hospital, Nara-Ken, Japan.)

Eighteen cases of cervical myelopathy are reported, due to posterior paravertebral ossification. These adult Japanese patients presented with symptoms of numbness of the hands and/or gait disorder related to spasticity of the lower extremities. No evidence of hereditary or familial etiology was obtained.

Roentgenographically the most characteristic feature of this type of spondylosis was dense ossification seen along the posterior longitudinal ligament extending from the first to the sixth cervical vertebral segment. The ossification was usually located in the upper cervical region along the middle of the posterior wall of the cervical vertebrae and usually protruded into the spinal canal, more at the level of each disk space. The disk spaces were preserved. The remainder of the ligamentous structures in the cervical area were roentgenographically normal. Myelography showed narrowing of the spinal canal, particularly at the level corresponding to the most prominent part of the calcification. Severity of symptomatology appeared to be directly related to the quantity and extent of the ossification or calcification. Serum calcium and phosphorus levels in several patients were normal. Histologically the specimens obtained revealed different stages of ectopic bone formation from unorganized calcification to true bone.

The majority of the patients required surgical decompression. In the authors' material this disorder accounted for approximately 1.7 per cent of all of their patients presenting with cervical symptoms.

The authors also discuss briefly other forms of cervical spondylosis and spondylitis and speculate as to the etiology of this paravertebral ossification.—*E. F. Binet, M.D.*

Djindjian, R., and Faure, C. Accidents medullaires de l'aortographie. (Spinal cord complications of aortography.) *J. belge de radiol.*, 1967, *50*, 207–213. (Address: Dr. Djindjian, 16 rue de l'Université, Paris VII^{e}, France.)

A number of papers been published during the past decade on the risks and complications of thoraco-abdominal aortography, as well as on the toxic effect of contrast agents on nerve tissue. The incidence of reported complications varies between 0.14 and 0.5 per cent.

The clinical manifestations of these complications are a sudden, usually irreversible flaccid paraplegia, preceded or accompanied by clonic contractions of the lower extremities. Extreme pain may be experienced by the patient if he is not anesthetized. There is loss of tendon and cutaneous (abdominal) reflexes, and of sphincteric control. The upper level of the paraplegia varies between D 8 and D 11. Death may result from urinary tract or pulmonary infection.

The pathologic findings are those of myelomalacia, demyelinization of the white matter and necrosis of the grey substance, predominantly in the region of the anterior horns. The area involved is that supplied by the anterior spinal artery of Adamkiewicz.

Injury to the cord is vascular in origin and may be due to: (a) ischemia—in translumbar aortography, injury to a vessel (subintimal or adventitial injection) near the orifice of a vessel; or in retrograde aortography, ischemia due to a thrombotic or dissecting lesion near the orifice of a vessel; and (b) arterial spasm—mechanical irritation by a needle or catheter; or chemical irritation by the contrast agent, causing ischemia and resultant loss of oxygen to the nerve tissue.

The least tolerated and most hazardous contrast agents are sodium acetrizoate and iodopyracet. The best tolerated are the diatrizoates—sodium, and the mixed sodium and methylglucamine. The increased tolerance of these new contrast agents by the kidneys and spinal cord accounts for the decreasing incidence of side reactions. Unfavorable reaction of the contrast agents may be related to the concentration and amount of contrast agent introduced in the artery.

With the patient in the decubitus position, there is better opacification of the arteries, since these arise from the posterior aspect of the aorta and their filling is favored by the "groove" effect of the contrast agent "settling" posteriorly.

One table, 1 reproduction of a roentgenogram and an excellent bibliography accompany this article.—*William H. Shehadi, M.D.*

Ulrich, H. The remote effects of cancer on the nervous system: pathology. *Proc. Roy. Soc. Med.*, July, 1967, *60*, 690–692. (From: The London Hospital Medical College, London, England.)

The pathology of the remote effects of malignant neoplasms on the nervous and muscular systems is as varied and complex as their clinical picture. Those involving the central and peripheral nervous systems fall into four main groups: (1) degenerative, (2) demyelinating, (3) inflammatory, and (4) necrotizing.

Of the degenerative syndromes the subacute cerebellar degeneration is the best known. The lesions consist of extensive disintegration and disappearance of Purkinje cells in the cerebellar cortex, occasionally associated with degeneration of the posterior columns and spinocerebellar tracts.

Not enough material has as yet been examined of the recently described syndrome resembling motor neurone disease. Of the 4 cases investigated so far only 1 resembled classic amyotrophic lateral sclerosis in that it showed severe degenerative changes both in the upper and the lower motor neurones, the latter largely confined to the lower brain stem and cervical cord.

Demyelination in the central nervous system occurs in progressive multifocal leukoencephalopathy. The lesions consist of numerous small foci of demyelination with preservation of axons and nerve cells.

The inflammatory neuropathies form a well-defined group of cases associated almost exclusively with oat cell carcinoma of the lung. The lesions occur in brain and cord, and consist of loss of neurones, focal and diffuse microglial activation, and intense lymphocytic infiltration of the perivascular spaces.

Necrotizing lesions have been described previously only in the spinal cord. The foci of myelomalacia may be scattered or confluent, leading to massive softening of the spinal cord.

Carcinomatous myopathies comprise three groups: (1) neurogenic, (2) degenerative, and (3) inflammatory.

Denervation atrophy with its characteristic pattern of atrophy of some motor units and preservation of others is not a primary disease of muscle but a response to destruction of the lower motor neurone.

The most common degenerative abnormality is severe atrophy of individual muscle fibers which is a nonspecific pattern and may occur in cachexia from any cause. The pattern becomes more significant when associated with other degenerative changes, such as vacuolation, hyalinization and necrosis of muscle fibers or the presence of regenerating fibers.

Acute polymyositis and dermatomyositis represent the inflammatory muscle diseases associated with malignant neoplasms, although only about 12 per cent of reported cases occur in conjunction with cancer. The histologic appearances vary, but in their florid form are highly characteristic: extensive necrosis of muscle fibers, dense lymphocytic infiltration and a tendency to fibrous scarring.

Electron microscopy of the lesions of progressive multifocal leukoencephalopathy reveals that the changes in oligodendroglial nuclei are due to the presence of virus particles. The lesions of the inflammatory type of carcinomatous neuropathy closely resemble those seen in common virus infections of the central nervous system. There is as yet no evidence to suggest that these lesions are due to a specific infection.

Autoimmune or hypersensitivity mechanisms have been advocated in the pathogenesis of polymyositis and some forms of demyelinating neuropathy. The evidence is slender, but emphasizes the need for further immunologic studies. There are pointers to metabolic factors being responsible for some myopathies. Further morphologic studies should be directed toward virologic, immunologic, and biochemical explorations.—*Lois C. Collins, M.D.*

WILKINSON, MARCIA, and CROFT, P. B. The remote effects of cancer on the nervous system: incidence and classification; clinical syndromes. *Proc. Roy. Soc. Med.*, July, 1967, *60*, 683-690. (From: The London Hospital Medical College, London, England.)

Malignant neoplasms may, by remote effect of unknown mechanism, produce a variety of neuropathies and myopathies. The incidence of such carcinomatous neuromyopathy in patients with malignant disease has been shown by a previous study to be approximately 6 per cent, and of these approximately 14 per cent occur in patients with carcinoma of the lung. The authors examined 1,465 patients with carcinoma of the lung, breast, ovary, uterus, cervix, prostate, stomach, colon and rectum. Although the incidence of neuromyopathy was considerably higher in patients with carcinoma of the lung than in all others, it was also high in patients with malignant disease of the ovary and stomach and relatively low in patients with malignant disease of the rectum, cervix and uterus. In 200 patients of the same age group who did not have known malignant disease, neuromyopathy was found in only 1 per cent.

Brain and Adams (1965) proposed a classification for carcinomatous neuromyopathy based on four major divisions: (1) encephalopathies, (2) myelopathies, (3) neuropathies, and (4) muscular disorders. The authors have divided the neuromyopathies into: (1) cerebellar degeneration, (2) myelopathy, (3) motor neurone type, (4) sensory neuropathy, (5) mixed peripheral neuropathy, (6) myopathy including myasthenia, and (7) neuromyopathy. They state that the neuromuscular disorders were by far the most common encountered in their series, but that exact classification was difficult because more than one part of the nervous system may be affected. The neurologic symptoms may develop either before, at the same time as, or after those of the neoplasm. The extent and severity of the neuromyopathy is independent of the size of the neoplasm.

Multifocal leukoencephalopathy is a condition occurring most commonly as a complication of lymphomas and leukemias and the diagnosis has usually been made only after death. It develops on a background of chronic disease, is insidious in onset and progressive, leading to death in a few months. The signs and symptoms indicate asymmetric disease of brain including mental disturbances, hemiparesis, loss of vision, dysphagia and dysarthria.

Diffuse polioencephalopathy may occur (1) with mental symptoms, either dementia or a fluctuating confusional psychosis, (2) with subacute cerebellar degeneration, which is uncommon but clinically very striking, or (3) with brain stem lesions which present a wide variety of signs and symptoms.

The myelopathies are largely indistinguishable from those of classic motor neurone disease, but usually the course is more benign. In a patient with symptoms suggesting motor neurone disease, it is imperative to try to exclude malignant disease, and if a tumor is found, the presence of an apparently incurable neurologic disorder should not be regarded as a contraindication to treatment of the carcinoma.

Massive necrosis of the cord occurs very rarely, and when present, is usually characterized clinically by an ascending flaccid paraplegia. Sensory neuropathy is also uncommon, is subacute in development and reaches a maximum in a few months following which it remains unchanged. The main disability is a gross sensory ataxia, crippling in nature. Peripheral sensory motor neuropathy is much more common and affects mainly the lower limbs with some degree of weakness, peripheral impairment of sensation and diminished tendon reflexes. Carcinoma of the lung accounts for about 50 per cent of the neuromyopathies of this type.

The muscular disorders consist of polymyopathy, myasthenia, dermatomyositis and endocrine disorders including ectopic ACTH syndrome, hyponatremia, hypercalcemia, hypoglycemia and carcinoid syndrome.

Pathogenesis of these syndromes remains obscure. In the endocrine disturbances there is good evidence that the tumor secretes a substance with biochemical activity resembling naturally occurring hormones. In progressive multifocal leukoencephalopathy, evidence of a virus infection is accumulating. In other forms of neuropathy an immune process has been suspected. Biochemical disturbances have been found in many of the patients. It seems probable that the diverse remote effects produced by carcinoma are not the result of a single pathologic process.—*Lois C. Collins, M.D.*

DI CHIRO, GIOVANNI, DOPPMAN, JOHN, and OMMAYA, AYUB K. Selective arteriography of arteriovenous aneurysms of spinal cord. *Radiology*, June, 1967, *88*, 1065–1077. (Address: National Institute of Neurological Disease and Blindness, Bethesda, Md. 20014.)

Myelography is not entirely satisfactory for the preoperative diagnosis of spinal cord vascular malformations since linear, serpiginous filling defects demonstrated by myelography are by no means constant or pathognomonic findings. In addition myelography may lead to false positive diagnoses such as in cases of tumor or other lesions with dilated vessels. Prompted by the diagnostic inadequacy of myelography, the authors initiated a commendable systematic angiographic study of spinal cord vascular malformations. The present report is based on the first 8 fully investigated cases.

A knowledge of the normal anatomy of the spinal cord vasculature is indispensable for an understanding of the pathologic anatomy of the lesions. The arterial supply of the spinal cord may be divided into two markedly different systems, the anterior and posterior. The anterior arterial chain, or anterior median spinal artery begins at the junction of the two anterior spinal branches of the vertebral arteries and extends downward along the entire anterior surface of the spinal cord to the filum terminale. Additional important contributions to the anterior chain, via anterior radicular arteries, occur in each region of the cord. For the cervical area, the anterior radicular branches originate from spinal branches of the cervical vertebral artery, while in the upper and middle thoracic cord they originate from spinal rami of the superior intercostal and aortic intercostal arteries. The lower thoracic and lumbar area is supplied by the great anterior radicular or great anterior medullary artery or artery of Adamkiewicz. This important artery may vary in origin from the spinal branches of the eighth intercostal to the fourth lumbar. The course of this artery is interesting in that, after a long course upward, it reaches the anterior aspect of the spinal cord, always above the lumbar enlargement. The vessel then divides into a thin ascending branch and a much larger descending branch which swings with a sharp "hairpin" bend to course downward on the midline. This last feature is clearly evident and distinctive on the angiographic illustrations. Actually, all the radicular arteries, except the anterior spinal rami from the vertebral arteries, behave like the artery of Adamkiewicz. This anterior arterial system supplies a two-third cross sectional area of the cord, including the corticospinal tracts.

The posterior spinal cord arterial system consists of two plexiform channels which course along each posterolateral surface of the cord and supply the posterior columns and posterior horns. These arteries originate from the posterior spinal rami of the postero-inferior cerebellar arteries as well as from the posterior radicular branches of the same spinal arteries from which the anterior radicular branches arise. This posterior system retains, to a large degree,

an embryonic plexiform pattern which covers the posterior cord surface like a net, and anastomoses between the posterior and anterior spinal arterial chains are abundant.

The suggested radiographic steps in studying such malformations, as derived from this study, are indicated in tabular form and carefully discussed. Essentially, the sequential approach should be plain roentgenography, then opaque myelography followed by angiography. The plain roentgenograms have not been contributory in the authors' series, to date. Iodophendylate myelography should be carried out with large amounts of contrast medium, 12 cc. or more, and prone and supine spot roentgenograms should be taken along with lateral cross table roentgenograms. Proper angiographic approach is essential for correct localization and consists of (a) preliminary mid-stream aortic injection to identify the approximate origin and possible multiplicity of contributing vessels, and (b) selective catheterization of each feeder to pinpoint the level of spinal entrance, to confirm the multiplicity of feeders, and to determine the relationship of the malformation to the cord itself. All studies are performed under local anesthesia. The technical aspect of catheterization is presented in detail along with the various contrast media employed with emphasis on the use of a methylglucamine salt for selective injection because of its low neurotoxicity.

The results of this study show that in over half the cases there was a single arterial feeder, generally entering at the upper segment of the vascular lesion. A mid-stream injection, unless it is close to the area of origin of the feeder, is unlikely to opacify the malformation. Therefore, proper placement of the catheter, based on vascular anatomy, is essential. No significant complication of angiography was noted, although 7 of the 8 patients experienced mild-to-severe spasms of the trunk and lower extremities with aortography, and 1 of the 7 showed a temporary deterioration of cord function as evaluated by postangiographic muscle testing. It is interesting that the selective injections never produced lower trunk or leg spasm.

The authors conclude that selective arteriography of arteriovenous aneurysms of the spinal cord is the method of choice to show the vessels feeding the malformation, and this demonstration is an indispensable preliminary step if surgical ligation of feeders is contemplated.—*Edward B. Best, M.D.*

Baker, Hiller L., Jr., Love, J. Grafton, and Layton, Donald D., Jr. Angiographic and surgical aspects of spinal cord vascular anomalies. *Radiology*, June, 1967, *88*, 1078–1085. (Address: Mayo Clinic, Rochester, Minn. 55901.)

The authors report a group of 13 patients studied, to demonstrate the presence of a vascular anomaly of the spinal cord, with the purpose of encouraging more wide-spread use of angiography and surgery in the management of spinal cord vascular abnormalities. This group was composed of 8 males and 5 females, ranging in age from 10 to 62 years. All had experienced progressive back pain and weakness in the legs for a number of months or years. The neurologic examination revealed the presence of upper motor neuron signs and a sensory level in all patients; the spinal fluid protein was elevated in all cases in which it was measured.

The radiologic investigation consisted of plain roentgenography followed by positive contrast myelography and subsequent angiography. Although plain roentgenograms gave little information, an abnormal myelogram was obtained in each patient and the findings led to angiography in all. The typical myelographic features of a vascular abnormality, media outlining abnormal vessels with partial or complete obstruction, were present in 11 cases, while the other 2 showed only obstruction in the lumbar region attributed to arachnoiditis. The angiography consisted of mid-stream catheter aortography with the tip of the catheter at the T 6 to T 8 level since the spinal cord was involved in the thoracic or lumbar region in all patients. Early in this study the catheter tip was positioned in the aortic arch but it was soon apparent that this location of the catheter tip produced poor visualization of the intercostal arteries. The authors recommend rapid serial studies in the anteroposterior and left posterior oblique position and subtraction techniques must be employed in the analysis of the films since some of the abnormal vessels are extremely tiny and otherwise might be ignored.

The authors' angiographic findings are quite interesting in that 3 distinct angiographic patterns were discernible and are designated as Type I, II, and III. The differentiation of these patterns is of considerable importance because of the therapeutic and prognostic implications.

A Type I pattern was obtained in 3 patients and consisted of 1 or 2 dilated intercostal arteries, of 5 to 10 mm. in diameter, supplying the posterior radicular branch. Although the intraspinal arterial component was insignificant, there was prompt opacification of huge intraspinous venous channels which constituted 80 to 90 per cent of the vessel bulk in the vascular anomaly. Drainage was through multiple dilated radicular veins into the azygos and hemiazygos veins.

In 7 patients a Type II pattern was seen which consisted of 3 to 5 abnormal intercostal and radicular arteries which never measured more than 3 mm. in diameter. They could be traced into the spinal canal, and along its length for 1 to 5 segments, where they joined in a "tuft"-like arterial network which was the main portion of the vascular anomaly. Invariably one feeding vessel was situated above and one below the arterial "tuft" with the others joining at

intermediate levels. Venous filling was delayed and the veins constituted less than 50 per cent of the anomaly.

The Type III arteriographic pattern was observed in only 1 case and was identical to that seen in Type II except that no veins were apparent at any time. This patient returned one year later, having previously refused surgical exploration, and at this time erosion of the lower dorsal vertebral bodies was evident. An ependymoma of the cauda equina was found at operation.

Eight patients who did not have severe longstanding and irreversible neurologic damage consented to surgery. The 3 patients in whom Type I angiographic patterns were found made remarkable recoveries. The other 5 patients, with Type II angiographic patterns, had less striking results and all were the same or only slightly improved in the immediate postoperative period. However, improvement has continued in these patients although many still have significant neurologic deficit. It is interesting that not one patient had deterioration in neurologic status in the postoperative period.

The authors conclude that catheter aortography, for suspected dorsal and lumbar vascular abnormalities, or retrograde brachial arteriography for cervical lesions, are the methods of choice for evaluating these lesions. Cine angiography will generally not depict small size vessels, while selective injection of one or several intercostal trunks increases the possibility of overlooking additional feeding vessels. The use of subtraction techniques in the routine roentgenographic analysis is essential in all cases and recognition of the distinctive angiographic pattern is of some prognostic importance. From the surgical point of view, the thoracic and intraspinal approaches to the abnormal feeding arteries are equally sound, but the intraspinal operation offers the additional advantage of direct inspection of the lesion and decompression of the subarachnoid space, if necessary.—*Edward B. Best, M.D.*

Skeletal System

Harris, D. Kenwin, and Adams, W. G. F. Acro-osteolysis occurring in men engaged in the polymerization of vinyl chloride. *Brit. M. J.*, Sept. 16, 1967, *2*, 712–714. (From: Northern Hospital, Liverpool, England.)

Two cases of acro-osteolysis in men engaged in the polymerization of vinyl chloride are described. The bones affected were the terminal phalanges of the fingers and the sacroiliac joints, but in one case the patella and in the other the phalanges of the feet were involved. The condition was accompanied by Raynaud's phenomenon and skin lesions.

Roentgenologically there were erosions of the phalanges, disruption of proximal interphalangeal joints, and cystic widening of the sacroiliac joints. Laboratory tests were essentially unremarkable.

The authors discuss the possible relationship to the collagen diseases, but they conclude that the condition is probably self-limiting.—*Arch H. Hall, M.D.*

Barsky, Arthur J. Macrodactyly. *J. Bone & Joint Surg.*, Oct., 1967, *49A*, 1255–1266. (Address: Albert Einstein College of Medicine, 1825 Eastchester Road, Bronx, N.Y. 10461.)

Macrodactyly is a congenital increase of *all* tissue elements of a digit which may occur in any locational combination, but the metacarpals are spared. Based on these criteria 56 cases were described previously in the literature; this report consists of 8 cases.

There are two forms of macrodactyly: (1) static, in which enlargement is present at birth and size increase with growth is proportional; and (2) true, in which growth occurs in a disproportionate fashion and is associated with an overgrowth of fatty tissue in the hand and forearm.

The author discusses possible etiologic factors and describes methods of management of the macrodactyly and associated deformities of syndactyly and curvatures.—*H. D. Davidson, M.D.*

Jones, J. Verrier, and Reed, Mervyn F. Paget's disease: a family with six cases. *Brit. M. J.*, Oct. 14, 1967, *2*, 90–91. (Address: J. Verrier Jones, Senior Medical Registrar, Bristol General Hospital, Bristol, England.)

This article records an English family in which 6 cases of Paget's disease have occurred in 3 generations.

Nine family members examined have no clinical evidence of the disease and their bone roentgenograms (limited to the pelvis and tibiae) and alkaline phosphatase are normal. Six of the 9 unaffected members, however, are between the ages of 17 and 29 years. It is expected that several of these will develop the disease in the fifth decade of life which is the average age of onset of the disease in this family.

A genealogic diagram and a table containing details of the individual members are presented. A bibliography stressing familial and hereditary aspects of Paget's disease is also appended.—*Everett H. Johnston, M.D.*

Specht, Elmer E. Rickets following ureterosigmoidostomy and chronic hyperchloremia: a case report. *J. Bone & Joint Surg.*, Oct., 1967, *49A*, 1422–1430. (Address: Box 0, Balboa Heights, Canal Zone 00101.)

Ureterosigmoidostomy is a fairly common operation, frequently performed in children for exstrophy of the bladder.

Hyperchloremic acidosis is a frequent complication following this surgery, but rickets as a further consequence is rare.

The author reports a child with exstrophy who had surgery at 2 years of age, bilateral ureterosigmoidostomy being performed. He was next seen by the author 9 years later. In the interim, he had not had good medical attention. On examination, he was seen to be small and underdeveloped. He had marked bilateral coxa vara, and striking bowing of both legs. Both wrists were broadened. Rachitic rosary and increased anteroposterior diameter of the thorax were noted. The exstrophy of the bladder was still present.

Initial laboratory studies demonstrated a hyperchloremic acidosis and, following treatment, including vitamin D administration and alkalinization therapy, the blood chemistry levels responded well.

Roentgenograms demonstrated severe rickets, which healed progressively during therapy. The patient had surgery for correction of valgus deformities of the femora and repair of the bladder exstrophy.

Follow-up study for over 2 years showed no recurrence of rickets either roentgenographically or histologically, despite the fact that the treatment was somewhat erratic. Serum chloride levels have been found to be elevated when medication has not been taken. Recent treatment included only alkalinizing therapy without vitamin D administration. This has seemed to control the condition satisfactorily.—*George L. Sackett, M.D.*

MILLER, BARRY, MARKHEIM, HERBERT H., and TOWBIN, MILTON N. Multiple stress fractures in rheumatoid arthritis: a case report. *J. Bone & Joint Surg.*, Oct., 1967, *49A*, 1408–1414. (Address: B. Miller, Honcho, Koganei-shi, Tokyo, Japan.)

The authors report a patient with severe rheumatoid arthritis who had a total of 9 stress fractures involving the lower extremities extending over a 7 year period. The patient had been on long term corticosteroid therapy. Her bones were markedly osteoporotic.

Stress fractures are not often reported in rheumatoid arthritis. The authors wonder whether this is due to the fact that they are rare, or whether they are not recognized and the pain is attributed to the underlying rheumatoid arthritis.

They review the literature on this subject and point out that the occurrence of stress fractures in patients with chronic arthritis has increased considerably since the introduction of steroid therapy.—*George L. Sackett, M.D.*

KING, JOE W., SPJUT, HARLAN J., FECHNER, ROBERT E., and VANDERPOOL, DON W. Synovial chondrosarcoma of the knee joint. *J. Bone & Joint Surg.*, Oct., 1967, *49A*, 1389–1396. (Address: J. W. King, Department of Pathology, Texas Medical Center, Houston, Texas 77025.)

This is a case report of a 43 year old man who had had painful swelling of the knee treated for 5 years. Initially, in December 1960, the symptoms were of painful swelling and the roentgenographic examination was normal. In May 1961, there were symptoms suggestive of a tear of the medial meniscus. At surgery, there was considerable fluid with numerous tiny cartilaginous appearing fragments. The pathologic diagnosis was synovial osteochondromatosis. Following this, the patient received radiotherapy to the knee. Pain and decreased motion became worse gradually. Roentgenograms in 1962 and 1963 showed calcified masses suggestive of osteochondromatosis. By 1966, these masses appeared more confluent and larger. There was no definite bone destruction. Surgery was performed at this time and following a pathologic diagnosis of synovial chondrosarcoma, an amputation was carried out.

Comparison of the histologic specimens of the operations in 1961 and 1966 showed many similarities in atypical cells which lead the authors to believe that the tumor was probably present originally and that the slow growth was characteristic of a tumor arising from the synovium.

The possibility of a change arising from the radiation therapy is also discussed.—*George L. Sackett, M.D.*

GOFTON, J. P., and TRUEMAN, G. E. Unilateral idiopathic osteoarthritis of the hip. *Canad. M. A. J.*, Nov. 4, 1967, *97*, 1129–1132. (Address: J. P. Gofton, M.D., Suite 10, 5780 Cambie Street, Vancouver 15, British Columbia, Canada.)

Primary osteoarthritis of the hip has been found in 3.4 per cent of persons over the age of 55 years. In two-thirds of these, the disease was unilateral. In patients studied for several years the unilateral form of primary osteoarthritis did not often progress to bilateral disease.

Primary osteoarthritis of the hip is classified according to the pattern of damage as follows: Medial-central or medial degeneration and narrowing; lateral narrowing of the superolateral area of the joint with or without minor subluxation; and mixed (not clearly medial or lateral), usually representing far advanced disease. The medial form of primary osteoarthritis in the majority of patients is found in both hips, while the lateral form is commonly limited to one hip. The lateral form is found in approximately 2 per cent of the population over the age of 55 years and may be a discrete form of degenerative disease.

It is generally assumed that the leg on the osteo-

arthritic side is shorter than the normal leg. The purpose of this paper is to demonstrate that this assumption is unfounded. The leg on the diseased side is, in fact, longer than the normal leg. The authors believe that this disparity contributes to the development of the disease.

The legs are measured roentgenographically with the patient standing on a level platform. Roentgenograms are made with the tube centered over the hip joints. The difference in height of the femoral heads is measured from a horizontal reference line. This was done in 14 patients with unilateral osteoarthritis of the "lateral type." Leg lengths were unequal in all 14 patients. In every instance the leg on the diseased side was longer. In a few additional patients with mixed or central osteoarthritis, no clear-cut association was evident between the site of disease and a long leg. In 4 patients the difference in length of the diseased leg and the normal leg was less than ¼ of an inch. As it is clear from the examination of the roentgenogram of a diseased hip that the disease has produced shortening, the original leg length disparity must therefore have been greater. An attempt was made to estimate the amount of shortening produced by the degenerative process. The width of the articular cartilage could be measured in the normal hip. This usually amounted to approximately ¼ inch. Comparison between the normal and diseased femoral heads allowed one to make an estimate of the amount of flattening. When these factors were taken into consideration, an original leg length difference was calculated. Of 14 patients with unilateral osteoarthritis 10 were considered to have an original leg length disparity greater than ½ inch.

Study of data of differences in leg length in the general population indicates that it is reasonable to postulate that no more than 15 per cent of the general population has a leg length disparity exceeding ½ inch. The finding of a disparity of this magnitude in either leg of 14 patients with unilateral osteoarthritis represents a very high incidence. This observation is meaningful because in all 14 patients the longer leg was on the diseased side. It is thus conceivable that the difference in leg length may have predisposed to the disease; *i.e.*, that the involved leg was originally longer than the uninvolved one.

A man with a leg length difference of ½ inch stands with a pelvic tilt of approximately 4 degrees. The pelvis is, therefore, adducted towards the long leg and abducted from the short one. Thus the hip on the side of the long leg is subjected to a greater stress than normally, while that on the short side is comparably spared. It is postulated that the cumulative effect of this increased stress on the hip of the long leg may be an important factor in the breaking down of joint cartilage and the degenerative changes which follow.

A minor degree of lateral subluxation of the femoral head is commonly seen in the lateral form of osteoarthritis. The pelvic adduction produced by a long leg would seem to favor lateral subluxation of the femoral head. It is reasonable to suspect that this minor subluxation is a secondary phenomenon.

Patients with a leg length difference of ¼–¾ inch are usually unaware of it. However, many develop a syndrome of pain in the buttocks, thigh, sometimes in the low back and occasionally in the calf. A large part of this distress is located at the insertion of the abductor muscles into the greater trochanter on the long leg side, suggesting that these muscles, as well as the hip are subjected to increased stress.

One of the most effective treatments for the relief of pain in the unilateral idiopathic osteoarthritis of the hip is a subtrochanteric osteotomy. This operation has numerous modifications. It is not clear how this operation relieves the pain of an osteoarthritic hip. Because most osteotomies shorten the leg, this factor alone may explain the relief of pain which in some instances follows this procedure.—*David Morse, M.D.*

LANGENSKIÖLD, A., and RISKA, E. B. Haematogenous Salmonella infection around a metal hip endoprosthesis. *Acta orthop. scandinav.*, 1967, *38*, 220–225. (From: The Orthopaedic Hospital of the Invalid Foundation, Helsinki, Finland.)

Infection occurring around a metal endoprosthesis is usually the result of inoculation of bacteria during surgery. However, in infections occurring several months to a few years later, it can seldom be proved whether inoculation took place at operation or not.

In the present case report, a Salmonella Newport infection arose around a Thompson type vitallium endoprosthesis 3½ years postimplantation for post-traumatic necrosis of the head of a femur. The signs of inflammation led to a hip joint tap from which the above named organism was cultured. It was felt that this had to be a hematogenous spread of infection, as the inflammatory process could be correlated with a gastrointestinal infection of an undefined nature which the patient had had in a Mediterranean country 1 month earlier, and this bacillus had not been cultured from any patient in Finland until it was cultured from this patient in 1963. It is therefore considered quite unlikely that the organisms were inoculated at the time of surgery in 1959. Intensive conservative therapy failed and the endoprosthesis was ultimately removed.

The question is raised whether there is a greater risk of hematogenous infection in tissues situated close to a metal implant than in other parts of the body. Certainly, the insertion of an endoprosthesis in a formerly infected area carries a risk of the flare-up of the infection. It is suggested that the possibility of hematogenous infection around large metal implants might deserve special prophylactic measures when there is a risk of bacteremia from general or local infections.—*Donald M. Monson, M.D.*

Kolář, Jaromír, Vrabec, Radko, and Chyba, Jiří. Arthropathies after irradiation. *J. Bone & Joint Surg.*, Sept., 1967, *49A*, 1157–1166. (Address: Dr. Jaromír Kolář, Radiological Clinic, Charles University, Prague 2, U nemocnice 2, Czechoslovakia.)

Radiation induced arthropathies were observed in 36 of 458 patients who developed osteodysplasia following therapeutic irradiation and 18 of 78 persons with radiation damage to the skin of the hands sustained in connection with their profession.

The depth dose to the joint necessary to produce changes is 2,800 rads or more with the 140 to 200 kv. apparatus. In the professional group the dose could not be estimated, but symptoms usually occurred in the average of 22 elapsed years after the start of exposure.

The main changes are: degenerative arthrosis, inflammatory arthritis and ankylosis. Degenerative arthropathy was found to be the most common.

The roentgenographic course was similar to that of other types of degenerative arthritis but rapidly progressive. The basis of these changes was degeneration and necrosis that developed in the joint structures and adjacent bones. Secondary septic arthritis occurred in some patients due to invasion by bacteria of low virulence resulting in ankylosis or amputation.

The joint must be considered to be radiosensitive. Unnecessary irradiation with too high doses should be avoided as low resistance after radiation damage may lead to serious infectious complication.—*Sumalee Chandaragga, M.D.*

Eaton, George O. Long-term results of treatment in coxa plana: a follow-up study of eighty-eight patients. *J. Bone & Joint Surg.*, Sept., 1967, *49A*, 1031–1042. (Address: 4 East Madison Street, Baltimore, Md. 21202.)

Eighty-eight patients with 100 hips of coxa plana were checked after treatment, the average follow-up being 19 years. All patients were examined by the author, had roentgenograms taken that were critically classified as to the results, including pain, motion and roentgen findings.

Three patients had arthrodesis, 37, 30 and $3\frac{1}{2}$ years after onset. Most patients were hospitalized until there was roentgen evidence of beginning regeneration of the head, and then they were fitted with an ischial caliber brace and high-shoe on the opposite foot. Excellent results were obtained in 46 per cent, good in 18 per cent, fair in 17 per cent and poor in 19 per cent.

The author found that the younger the patient at the onset, the better the prognosis. The time lapse between onset of the symptoms and treatment did not appreciably influence the results. Patients with less than 6 months bed-rest had the lowest percentage of good results but, conversely, prolonged bed-rest did not insure good results (13 of 18 patients treated by none or less than 6 months of bed-rest had excellent or good results). The severity of symptoms and findings at onset did not correlate with the final results. With bilateral disease (24 hips), the result was usually the same in each hip and 18 of the 24 gave good or excellent results on follow-up examination. The disability and symptoms did not appear to progress in the 20 and 30 year follow-up studies.

The outcome of treatment could not be predicted but conservative recumbent treatment gave a high percentage of good or excellent results.—*Martha E. Mottram, M.D.*

Mitchell, George E., Lourie, Herbert, and Berne, Alfred S. The various causes of scalloped vertebrae with notes on their pathogenesis. *Radiology*, July, 1967, *89*, 67–74. (Address: 736 Irving Avenue, Syracuse, N. Y. 13210.)

A normal slight concavity of the dorsal surface of vertebral bodies exists and "scalloping" is an increase of this concavity.

The authors classify scalloping according to pathogenic mechanisms which cause alteration of bone: (1) increased intraspinal pressure localized or generalized, (2) dural ectasia, (3) small spinal canal, (4) congenital skeletal disorders, and (5) normal variants. "Hemi-scalloping" may occur from pressure on a single pedicle.

Normal variants of physiologic scalloping tend to occur in the lumbar area and pathologic scalloping elsewhere.

Tumors and cysts usually produce widening of interpediculate distance first and scalloping later due to protection of the vertebrae by the dorsal longitudinal and annular ligaments. Scalloping is most apt to occur with large slow growing lesions in the caudal portion of the spinal canal during active growth.

Dual ectasia is due to loss of intact strong dura from such as seen in the Ehlers-Danlos syndrome.

Bone dysplasia causes a small spinal canal and scalloping appears usually in the lumbar area.

The mechanism of scalloping in congenital skeletal disorders, as Morquio's disease and Hunter-Hurler syndrome, is uncertain but it may be that the vertebrae are unable to withstand even the normal dural pulsations over the posterior surfaces. Both are known to involve inborn disorders of mucopolysaccharide metabolism.—*C. T. Edmondson, M.D.*

Doty, Donald B., Treiman, Richard L., Rothschild, Philip D., and Gasper, Max R. Prevention of gangrene due to fractures. *Surg., Gynec. & Obst.*, Aug., 1967, *125*, 284–288. (From: The Vascular Surgery Service

of the University of Southern California School of Medicine, Los Angeles County Hospital, Los Angeles, Calif.)

There does not seem to be a general appreciation of the fact that gangrene develops in nearly all patients with a fracture which produces major arterial trauma, if that arterial trauma is not corrected. Gangrene develops from almost all posterior dislocations of the knee if arterial exploration is not performed. Amputation is the end result in nearly all of these patients.

It is axiomatic that the possibility of arterial injury must be suspected to initiate proper therapy. The popliteal, brachial and femoral arteries were most frequently injured in a series reviewed at the Los Angeles County Hospital in the years from 1948 to 1963. A high index of suspicion must be directed to those sites of the body where large arteries are in close proximity to bone. These vessels include the subclavian artery beneath the clavicle, the brachial artery adjacent to the shaft and supracondylar portion of the humerus, the femoral artery near the shaft of the femur, and, in particular, the popliteal artery. If there is the least doubt concerning the continuity of the arterial system of an extremity, arteriography should be performed. Preferably, the arteriography should be carried out before reduction of the fracture or dislocation. A diagnosis of arterial spasm demands that the surgeon prove arterial patency. When obstruction, spasm, or sharp angulation of the artery is seen on the arteriogram, exploration of the artery is mandatory.

Once arterial continuity has been restored, peripheral pulses must be carefully evaluated together with color, temperature and capillary filling of the hand or foot. If the peripheral pulse is not present at the completion of the operation, or if the pulse later disappears, or if signs of ischemia develop, patency of the arterial system must be demonstrated by arteriography. Failure to demonstrate patency demands re-exploration. This is mandatory if gangrene and limb loss are to be prevented.

In summary, observance of the following principles will prevent the unwarranted loss of limb: a high index of suspicion and prompt recognition of arterial injuries in fractures and dislocations, particularly those about the knee; rejection of the concept of arterial spasm; prompt arteriography with critical interpretation, particularly of spasm; prompt exploration of the involved arteries; precise repair of the injured vessel; proximal and distal thrombectomy with the Fogarty embolectomy catheter; postoperative arteriography; and prompt reoperation in all patients in whom arterial insufficiency recurs after arterial repair.—*Douglas S. Kellogg, M.D.*

Astley, R. Arthrography in congenital dislocation of the hip. *Clin. Radiol.*, July, 1967, *18*, 253–260. (From: The Children's Hospital, Birmingham, England.)

The major cause of obstruction in congenital hip dislocation is inversion of the fibro-cartilaginous rim of the acetabular fossa—the labrum or limbus. Arthrography is a useful aid, because it indicates the type of case in which open reduction may be advisable. The earlier the diagnosis of congenital dislocation is made, the greater is the possibility of a good reduction.

The examination is carried out under a general anesthesia. The "frog position" with the thighs abducted to a right angle is preferable for the injection. Following the preliminary roentgenogram, a lumbar puncture needle is introduced under the adductor tendons and directed more or less horizontally in a cranial direction, using momentary fluoroscopy to check the needle's position in relation to the femoral neck, or quite close to the head. Following attainment of the correct position, a small amount of dilute contrast material such as 25 per cent hypaque is injected. This quickly flows around the periphery of the joint. Filling must be good but not so dense that filling defects, mainly anteriorly and posteriorly, are obscured. If there is already plaster-fixation, an anteroposterior roentgenogram in the "frog position" plus a slightly oblique roentgenogram may be all that can be taken. If no fixation is present, roentgenograms in internal rotation, the neutral position, external rotation and in abduction may be made.

Within the main mass of contrast medium a translucent area indicates the cartilage of the femoral head, around its ossification center. In the normal infant there is a roughly triangular filling defect at the outer lip of the acetabulum—the fibrocartilaginous rim of the cavity, this being the normal glenoid labrium or limbus. Occasionally eccentric ossification of the femoral head may give a false impression of displacement, but the true position can be readily demonstrated by arthrography.

Where an inverted limbus is present with a non-reduced dislocation, on arthrographic examination the capsule is visualized as a bilocular or hour glass shape, with one loculus around the head and one in the acetabulum. The upper part of the constriction between the two loculi is due to the inverted limbus. Where the femoral head is in more nearly correct position the inverted limbus appears flatter and as a narrow V-shaped filling defect between the translucent cartilaginous head and the acetabular roof.

In some cases the inverted limbus atrophies following conservative treatment and open reduction is not necessary. Most of the author's cases were first diagnosed between the ages of 1 and 2 years. In view of the fact that emphasis is now on the diagnosis of congenital dislocation in the newborn period, the need for arthrography will diminish

but may still be required for the occasional case, particularly when diagnosed in older children.—*Samuel G. Henderson, M.D.*

BLOOD AND LYMPH SYSTEM

PARKINSON, D., MACPHERSON, R. A., CHILDE, A. E., MIDDLECOTE, L. R., MORROW, I. M., and MACEWAN, D. W. Routine simultaneous bi-plane stereoscopic angiography. *J. Canad. A. Radiologists*, Sept., 1967, *18*, 371–376. (From: Departments of Neurosurgery and Radiology, The Winnipeg General Hospital, Winnipeg; and the Picker X-Ray Engineering Ltd., Winnipeg, Manitoba, Canada.)

The authors describe an apparatus for obtaining simultaneous bi-plane stereoscopic angiograms. The description of the apparatus is complete and the interested reader should consult the original article. The operation is quite similar to routine bi-plane angiography with only a few minor modifications. Proper cones and meticulous positioning are required since a light collimator is not available because 2 x-ray tubes $4\frac{7}{8}$ inches apart are mounted together for each plane. When angulation of tubes is required, they are manually angled and maintained in position by a metal wedge.

The authors have performed 2,000 examinations in the past 2 years and can do both carotid studies using only 24 cc. of contrast material combined with 90 second film processing. A great deal of procedure time has been saved.

Stereoscopic films have been useful in the following situations: (1) differentiating small berry aneurysms from end-on vessels; (2) determining the relationship of berry aneurysms to the adjacent vessels; (3) separating vessels entering and leaving arteriovenous malformations from nearby vessels; (4) separating neck vessels; (5) in peripherally situated pulmonary emboli; and (6) in abdominal aortography, including selective studies of major abdominal aortic branches.

The over-all increase in cost was only 17 per cent.—*James R. Stevenson, Major, MC*

WHOLEY, MARK H., and BOCHER, JACK. Angiography in musculoskeletal trauma. *Surg., Gynec. & Obst.*, Oct., 1967, *125*, 730–736. (From: The Departments of Radiology and Orthopedic Surgery, University of Pittsburgh School of Medicine, The Veterans Administration Hospital and Allegheny Valley Hospital, Pittsburgh, Pa.)

The clinical differentiation of arterial spasm, thrombosis, or laceration following skeletal trauma is frequently impossible. Emergency arteriography can be extremely helpful during the initial skeletal survey or coincident with surgical repair. In arterial laceration, excessive delay in treatment results in irreversible ischemic changes. Since the morbidity of arteriographic examination is negligible, more widespread application of this procedure is recommended.

A high index of suspicion of arterial injury is warranted in fractures of the distal femur, proximal tibia and distal humerus. Vascular injuries can accompany medial clavicular fractures, anterior humeral dislocations, and severe pelvic fractures. It is also known that gradual axillary artery occlusion can accompany prolonged use of crutches.

Radiologists should encourage the use of emergency arteriography with the hope of reducing the amputation rates in severe musculoskeletal trauma.—*Arch H. Hall, M.D.*

KESSLER, RICHARD E. The umbilical vein in diseases of the liver. *Bull. New York Acad. Med.*, Nov., 1967, *43*, 977–984. (From: Department of Surgery, New York University School of Medicine Surgical Service, Manhattan Veterans Administration Hospital, New York, N. Y.)

Catheterization of the remnant of the umbilical vein provides a convenient method to measure the portal pressure and visualize the portal venous system by angiography. It supplements percutaneous splenoportography if that procedure is technically unsatisfactory, if it fails to visualize the portal vein, if splenic puncture is not possible after splenectomy, or is contraindicated by the presence of ascites or a hemorrhagic diathesis.

Catheterization of the umbilical vein is the procedure of choice in patients with liver metastases in order to obtain serial hepatograms as a means of measuring the therapeutic efficacy of anticancer drugs. In patients with cirrhosis of the liver and bleeding esophageal varices who are not candidates for a major surgical procedure, an umbilical vein catheter is used to study the response of the portal pressure to conservative modalities such as vasopressin, thoracic duct lymph drainage, and gastric hypothermia.

The catheters have been *in situ* for as long as 5 weeks without complication in patients without cirrhosis. On the other hand, the portal pressure has been measured more than 300 times in a single patient during an 11 day period, while observing the response of the portal pressure to drainage of lymph from the thoracic duct.

Excellent portohepatograms can be obtained when a contrast medium is injected through an umbilical vein catheter and may demonstrate lesions as small as 0.5 cm. in diameter. This permits percise measurement of the hepatic tumors in evaluating the therapeutic efficacy of anticancer drugs when the tumors are most vulnerable.

In this series of 100 consecutive attempts at catheterization of the umbilical vein, there were 9 failures, with the last 75 attempts having only 4 failures. The procedure is performed under local anesthesia in 15 to 30 minutes. In these 100 patients, there have been 4 relatively minor complications. The one major complication that occurred was in a patient who had cirrhosis of the liver and partial thrombosis of the portal vein demonstrated by the umbilical vein angiography. Eight days after catheterization, the patient died of hepatic failure. An autopsy revealed complete thrombosis of the portal vein, and it is believed that the umbilical vein catheterization may have contributed to the propagation of the existing thrombus.—*Donald M. Monson, M.D.*

TAYLOR, G. W. Chronic lymphoedema. *Brit. J. Surg.*, Oct., 1967, *54*, 898–900. (From: Department of Surgery, St. Bartholomew's Hospital, London, England.)

Chronic lymphedema may be primary (congenital) or secondary (acquired) in origin. Regardless of etiology, lymphedema is due to fluid and protein retention in tissue spaces because of inadequate lymphatic pathways. Normally the lymphatics act as a drainage route for tissue fluids and remove from the interstitial space large molecular size substances and plasma proteins that have leaked into the tissues. Accumulated extravascular protein leads to abnormal osmotic tension and interstitial water accumulation or edema. Secondarily, tissue fibrosis and hyperkeratosis may develop in chronic cases and prolonged stretching of the skin results in loss of tissue elasticity which may further encourage edema.

Recurrent cellulitis of streptococcal origin and lymphangiosarcoma, most frequently associated with postmastectomy edema of the arm, are complications of chronic lymphedema. Lymphangiosarcoma presents as reddish-purple skin nodules that coalesce and spread by lymphatic and hematogenous routes. Another condition, chylous reflux, is the result of retrograde flow of chyle into serous cavities, the renal tract, or chyle containing vesicles of the limbs.

Treatment of lymphedema is usually conservative. Night elevation of the limb, constant wearing of properly fitting elastic stockings, and intermittent diuretic therapy are most often used. If the degree of edema is more than a cosmetic problem and interferes with function, or fibrous tissue formation prevents shrinkage with conservative treatment, surgery may be indicated. Primary lymphedema can be reduced by the wide excision of edematous subcutaneous tissue with techniques such as described by Charles and Thompson. Surgical treatment of secondary lymphedema is limited to those patients in whom the original disease is inactive and swelling is burdensome. The techniques described above are used as well as the construction of artificial lymphovenous shunts.—*John T. Underberg, M.D.*

VINEBERG, ARTHUR M., and SYED, A. K. Arterial vascular pathways from subclavian arteries to coronary arterioles created by free omental myocardial implants: a preliminary report. *Canad. M. A. J.*, Aug. 19, 1967, *97*, 399–401. (From: Department of Surgery, Royal Victoria Hospital, and the Department of Experimental Surgery, McGill University, Montreal, Quebec, Canada.)

Cardio-omentopexy—the term for applying the omentum to the myocardial surface—has been used in patients suffering from cardiac ischemia. Originally, the omentum was left attached to its abdominal blood supply. In subsequent animal experiments, strips of omentum were implanted into the myocardium, leaving the omental strips attached to the vascular pedicles in the abdomen. In 1960 it occurred to one of the authors of this article that if the omentum was deprived of its blood supply it would seek out a new one. Since 1962 the authors have used the free omental graft to supplement internal mammary artery implantation done for myocardial revascularization in human subjects. In previous studies it was shown that the free omental graft when placed in the vicinity of a vessel will form communications with such vessels as those of the spleen, liver, intestinal arteries, thoracic wall, internal mammary artery, superior epigastric, ascending aorta and the coronary vessels. This happens with and without epicardiectomy, although such communications form more actively after epicardiectomy has been done.

In 1966 the authors began to thread strips of omentum through the right and left ventricular walls, at the same time constricting the anterior descending and circumflex coronary arteries by ameroid constrictors placed around their main stems. Since that time, it has been confirmed in 75 animal experiments that a completely new set of intramyocardial vascular channels can be established within 8 days by this procedure. The arteries in the omental strip rapidly make connection with surrounding arterioles so that the right coronary artery blood flows immediately through vessels in the omental strip to relieve the ischemic area produced by the ameroid constrictors placed on the coronary vessels. Following this demonstration, the authors decided to bring subclavian arterial blood to the myocardium through free omental strips implanted into the wall of both ventricles. This was done by suturing a one-half inch strip of greater omentum to the right and left subclavian arteries, after removing the pleural and endothoracic fascia covering these arteries. The distal end of the omental

strip is threaded through the left and right ventricular walls, respectively.

The authors' experience with over 450 revascularization operations on patients has made it clear that a new source of systemic arterial blood is needed for myocardial revascularization.—*Douglas S. Kellogg, M.D.*

DeLorimier, Alfred A., Simpson, Ellen B., Baum, Richard S., and Carlsson, Erik. Hepatic-artery ligation for hepatic hemangiomatosis. *New England J. Med.*, Aug. 17, 1967, *277*, 333–337. (From: Departments of Surgery, Pediatrics and Radiology, University of California School of Medicine, San Francisco, Calif. 94122.)

The involuting hemangioma (capillary hemangioma or hemangioendothelioma) of childhood is a congenital vascular malformation, which progressively enlarges in early infancy, becomes stationary for a variable period and then spontaneously regresses. About 60 per cent of all cutaneous lesions are present at birth; the remainder become evident within 2 months after birth. They attain their maximum growth in the first 6 months in half the cases, and in 6 to 12 months in the rest.

The typical diagnostic triad is as follows: multiple enlarging cutaneous hemangiomas; hepatomegaly; and congestive heart failure. Only 3 of 25 patients described since 1932 have survived after conservative treatment of heart failure. Respiratory distress occurred within 6 weeks after birth in half the cases. These infants usually died within 2 weeks. In all the fatal cases, death occurred within 6 months after birth. Only 3 of the babies survived after congestive heart failure. The clinical course of these 3 patients suggests that the heart failure occurred when the tumor had attained its maximum size.

These hepatic hemangiomas produce a wide open conduit between the hepatic artery and veins. An arteriovenous fistula initially reduces the blood pressure, accelerates the pulse rate, increases the venous filling of the heart and raises the cardiac output. Since these hemangiomas diffusely involve the liver, they cannot be resected readily by hepatic lobectomy, and the large arteriovenous shunt can be decreased only by ligation of the main hepatic artery. Ligation of this artery proximal to collateral branches does not obliterate all arterial inflow into the liver, for collateral vessels from the left gastric artery and superior mesenteric artery provide blood supply to the proper hepatic artery.

The authors include a case report of a baby girl, 16 days old, admitted to hospital because of severe respiratory distress. The pulse was 170, the respirations 120, and the blood pressure was 150/40. Roentgenograms showed generalized cardiac enlargement, increased pulmonary vascularity and congestion. Celiac arteriography revealed a large hepatic artery and pooling of contrast material in vascular lakes throughout the liver, most pronounced in the right lobe. The rapid growth of the hemangiomas suggested the possibility of early death from heart failure. Four days after admission the hepatic artery was ligated at its origin from the celiac artery, proximal to the right gastric and gastroduodenal branches. After operation the patient improved. The blood pressure was 94/45 to 108/60; the pulse was 120; and the respirations 40 to 60. A roentgenogram of the chest showed a decrease in heart size and pulmonary vascularity. She was discharged from hospital 2 weeks after surgery. She is alive and well at present, with normal growth and development.—*Douglas S. Kellogg, M.D.*

Ferris, Ernest J., Vittimberga, Frank J., Byrne, John J., Nabseth, Donald C., and Shapiro, Jerome H. The inferior vena cava after ligation and plication: a study of collateral routes. *Radiology*, July, 1967, *89*, 1–10. (From: Boston City Hospital, 818 Harrison Avenue, Boston, Mass. 02118.)

Thirty patients were studied venographically after plication or ligation procedures on the inferior vena cava. Four major routes are available for return of blood from the pelvis and lower extremities after occlusion of the inferior vena cava: (1) central, (2) intermediate, (3) portal and (4) superficial.

The central ascending lumbar vertebral plexus is the most important collateral network. The *central* channels are composed of the ascending lumbar, internal and external venous plexus, hemiazygos-azygos system, and the vena cava above the level of occlusion. The *intermediate* channels comprise the ovarian-testicular veins, the ureteric veins, and the left renal-azygos system. All these veins, especially the ureteric veins, may attain a huge size. The *portal* system serves as a collateral channel for the obstructed vena cava. Filling is via the superior hemorrhoidal anastomosis with the middle and inferior hemorrhoidal plexus. The superficial routes are extensive. In general, the inferior epigastric veins drain superiorly into the internal mammary veins. The *superficial* epigastric and circumflex iliac veins drain via the thoracoabdominal veins, and the lateral thoracic vein into the axillary vein.

Thirty patients were studied. The time of study varied from 2 days to 2 years. Venous pressures and circulation times were obtained and compared with those of the antecubital vein. Sixty cubic centimeters of 60 per cent contrast medium was injected by hand or pressure injector through a catheter introduced into one or both femoral veins. Serial roentgenograms in the anteroposterior and lateral projections were obtained. In 2 cases, because of bilateral femoral vein thrombosis, intraosseous venography was performed.

In all cases of ligation, the vena cava immediately above the tie was seen and not a single case of thrombus was observed at this level. The vena cava below the tie was thrombosed in 10 of 20 cases. In 5 of 20 cases only one common iliac vein was patent.

Eight patients had plications of the inferior vena cava and two had teflon clips. The plications tended to remain open early. In only 1 of 5 patients studied during the first 6 months, was the vena cava thrombosed below the plication and the openings closed. In 5 patients studied between 6 months and 2 years after surgery, there was patency in only 2. Only 3 of 9 patients studied maintained a patent plication.

Elevated venous pressure and prolonged circulation time in the femoral vein tended to parallel the onset of leg edema, or an increase in pre-existing edema. Recurrent pulmonary embolism after ligation occurred in 3 cases.—*A. W. Sommer, M.D.*

MAVOR, G. E., and GALLOWAY, J. M. D. Collaterals of the deep venous circulation of the lower limb. *Surg., Gynec. & Obst.*, Sept., 1967, *125*, 561–571. (From: The Aberdeen Royal Infirmary, Aberdeen, Scotland.)

The authors state that current textbook descriptions of the venous anatomy of the lower limb are imcomplete and even inaccurate. They dissected 22 lower limbs and found direct and indirect communications between the major veins of the leg below the termination of the profunda femoris vein. They studied venograms of the lower extremity and found the collateral venous system of the pelvic vessels to be inadequate.

This evidence is used to show that venous occlusion of the deep veins can be separated into the iliofemoral thrombosis (above the termination of the profunda) and the femoral popliteal thrombosis (below the termination of the profunda femoris vein).

In peripheral venous thrombosis (femoral popliteal), there is no venous insufficiency, and conservative therapy is indicated. In distal venous thrombosis (iliofemoral), the collateral circulation is often inadequate and a venous thrombectomy is indicated. —*Richard P. Taylor, M.D.*

GENERAL

O'MARA, ROBERT E., RUZICKA, FRANCIS F., JR., OSBORNE, ALAN, and CONNELL, JAMES, JR. Xeromammography and film mammography: completion of a comparative study. *Radiology*, June, 1967, *88*, 1121–1126. (Address: 153 W. Eleventh Street, New York, N. Y. 10011.)

The authors present the results of a comparative study of 463 breast examinations which were done by means of xeromammography and film mammography. Of the 463 cases, 162 had a biopsy proven diagnosis and the diagnostic accuracy of the two procedures was found to be very similar.

The details regarding the basic principles of xeromammography have been previously described by the authors (*Radiology*, 1965, *85*, 260–269). One great advantage found with the use of xeromammography is that of a lower patient x-ray exposure. The skin dosage received by the patient is approximately one-third that incurred with the film technique. Other advantages include the ability to see all structures on a single image, and a sharp delineation of even small differences in glandular structures. The "edge effect" produced by accentuation of the edges of tissues of differing densities plus the low-contrast range of the method enable one to see all structures, from soft tissues to calcification and bone, on a single exposure.

Several problems have been encountered in the technical aspects of xeromammography. These include: (a) imperfections in the selenium plate which at times closely resemble calcifications; (b) moisture absorption by the acetate coating on the plate in humid weather, resulting in uneven distribution of the developing powder; (c) moisture absorption by the developing powder which causes clumping of the powder; (d) attraction of dust particles to the charged plate, simulating calcifications; and (e) the relatively primitive design and cumbersomeness of the equipment available.

It is the authors' opinion, however, that these technical difficulties will lessen with continuous improvement in design as the equipment and technique become more refined.—*Donald N. Dysart, M.D.*

RADIOISOTOPES

ROSENTHALL, LEONARD, MATHEWS, GEORGE, and STRATFORD, JOSEPH. Radioxenon brain scanning with the gamma-ray scintillation camera. *Radiology*, Aug., 1967, *89*, 324–328. (From: Division of Nuclear Medicine, Montreal General Hospital, Montreal 25, Quebec, Canada.)

Previous studies of cerebral blood flow have been made by monitoring the disappearance rates of Xe^{133} and Kr^{85} from the brain. The desaturation curves obtained with Xe^{133} consist of 2 or 3 exponential components; a fast component with a $1\frac{1}{2}$ minute half life, and a slower component with a 10 minute half life, representing the cortical and white matter blood flow, respectively.

The short imaging time of the scintillation camera (Pho/Gamma, Nuclear-Chicago), 30 seconds for the dose of Xe^{133} used here, permitted the use of Xe^{133} as a scanning agent. The Xe^{133} was administered either by the injection of 10 mc dissolved in 10–20 ml. of saline into the carotid artery or by the inhalation of about 15 mc through a closed system

breathing device. Serial scintiphotos were made during the washout period. Whenever possible, comparisons were made with the brain scan obtained with macroaggregates of radioiodinated albumin (MARIA). This was injected into the carotid artery following the xenon solution study. Approximately 150 μc of I^{131} containing about 1 mg. of albumin with particle size of 5 to 30 microns in diameter was the usual dose.

The results of scans of 6 patients indicate that the diffusion of Xe^{133} into relatively avascular and cystic tumors did not differ greatly from that in the adjacent tissue. This diffusibility of the Xe^{133} gas could lead to a loss of resolution of small lesions which would otherwise be detected with MARIA as a test agent.

No deleterious reactions from the 70 intracarotid injections of MARIA were encountered. Radioxenon, being entirely innocuous should be completely safe.

The authors' experience, based on a limited study, indicated that a broad spectrum of desaturation curves can be anticipated contingent on blood flow, necrosis, and xenon diffusibility within the lesion. One of the main advantages of the MARIA scan is its ability to detect and localize small cerebral vascular accidents when the cerebral angiogram is normal. The intracarotid injection of Xe^{133} will do the same, even though the gas may dissolve in the lesion. More work is required before a final assessment of the Xe^{133} brain scan is justified.—*L. H. Deiterman, Jr., Ph.D.*

Quinn, James L., III, and Brand, William N. Pertechnetate-99m thyroid scans obtained incidental to brain scans. *J. Nuclear Med.*, July, 1967, *8*, 481–486. (From: Department of Radiology, Northwestern University School of Medicine and the Nuclear Medicine Laboratory, Chicago Wesley Memorial Hospital, Chicago, Ill.)

Thyroid scans were done on 767 patients who primarily were having brain scans using pertechnetate 99m. Patients with known thyroid disease, or previous thyroid surgery, were excluded. The thyroid scan was begun 10 to 30 minutes after injection of 65 μc of pertechnetate 99m per pound of body weight.

The scans were coded as satisfactory or unsatisfactory. The satisfactory scans were further coded as normal, nodular and inhomogeneous.

Six hundred-four (78.7 per cent) of the scans were satisfactory. There were 143 (18.6 per cent) normal, 223 (29 per cent) nodular, and 238 (31 per cent) inhomogeneous scans. The inhomogeneous scans were thought to be due to insufficient data recording and incomplete resolution of smaller nodules.

Multinodularity by scan increased with age and was greater in females, with 40 per cent occurring in the 61 to 70 age group. The per cent of normal scans decreased with age. The inhomogeneous scans had a random age distribution, and the incidence was higher in males.

I^{125} and pertechnetate 99m scans were done in several cases, and the I^{125} scans were superior. This was thought to be due to the pertechnetate scans imaging only a trapping function, while the iodine scans record the net effect of trapping, organification and release.—*Charles W. Cooley, M.D.*

Hagen, Garrett A., Ouellette, Robert P., and Chapman, Earle M. Comparison of high and low dosage levels of ^{131}I in the treatment of thyrotoxicosis. *New England J. Med.*, Sept. 14, 1967, *277*, 559–562. (From: Department of Medicine, Harvard Medical School, and the Medical Services and Physics Research Laboratory, Massachusetts General Hospital, Boston, Mass. 02114.)

Permanent hypothyrodism occurs not infrequently in the treatment of hyperthyrodism with I^{131}. The reproductive capacity of the thyroid cells is damaged by the irradiation, resulting in a diminishing number of cells.

Two dosage levels of I^{131} were given to a series of patients with hyperthyrodism to evaluate the effect of lower dosages of I^{131}. The usual clinical dose of 160 μc of I^{131} per gram of thyroid was given to 40 hyperthyroid patients; and 80 μc of I^{131} per gram of thyroid was given to 116 hyperthyroid patients. Five drops of a saturated potassium iodide solution were administered orally each day in the lower dosage groups 2 weeks after treatment.

The dose in the high dosage group was 7.4 ± 2.4 mc of I^{131}. There were 33 per cent hypothyroid and 40 per cent euthyroid patients in this group. Twenty per cent required additional I^{131}, and 7 per cent were controlled with potassium iodide or antithyroid drugs.

The dose in the lower dosage group was 3.6 ± 0.9 mc of I^{131}. Six per cent of patients became hypothyroid and 70 per cent were euthyroid. Fourteen per cent of the cases required 2 or more doses of I^{131}.

Potassium iodide was helpful in controlling patients with mild persistent thyrotoxicosis after I^{131} until the full effect of the radiation took place. It was possible to avoid retreatment with I^{131} in 6 per cent of the cases.

The lower dosage level of I^{131} combined with the prolonged use of potassium iodide in the treatment of thyrotoxicosis resulted in a definite decrease in the incidence of hypothyrodism without an increase in the number of retreatments during the two year study. Seventy-seven per cent of the cases were euthyroid after 4 months.—*Charles W. Cooley, M.D.*

Mariani, M., Maseri, A., and Giuntini, C. Precordial counting compared with arterial sampling for measuring the cardiac output in man. *J. Nuclear Biol. & Med.*, April–June, 1967, *10*, 66–71. (From: Group of Clinical Physiology and Center of Nuclear Medicine, Medical Clinic, University of Pisa, Italy.)

Simultaneous cardiac output determinations with the pericardial count method and arterial sampling technique following a single injection of I^{131} tagged human serum albumin through a preloaded cardiac catheter were compared in 69 instances.

The cardiac output with pericardial counting averaged 9.14 L./min. and those obtained with arterial sampling 8.98 L./min. Sixty-five determinations fell within or on the line representing $\pm$ 20° deviations from the line of identity.

It has been stated that the critical factors in the determination of the cardiac output by pericardial counting are the site of administration of the albumin which should be close to the right atrium and the use of a fairly narrow collimator. Using this technique, pericardial determinations of cardiac output appear to be an accurate method even in the presence of variation of cardiac size and blood flow.—*A. M. Rejali, M.D.*

Williams, Donald F., and Blahd, William H. The diagnostic and prognostic value of strontium-85 photoscanning in carcinoma of the prostate. *J. Urol.*, June, 1967, *97*, 1070–1074. (From: Department of Surgery, Division of Urology and the Department of Medicine, University of California Center for the Health Sciences, and the Department of Surgery, Urology and Radioisotope Services, Wadsworth Veterans Administration Hospital, Los Angeles, Calif.)

Radioactive strontium 85 photoscans can detect metastatic disease prior to roentgenographic bone changes in patients with carcinoma of the prostate.

In this series of randomly selected patients with clinically proven adenocarcinoma of the prostate 20 per cent had negative roentgenograms with positive photoscans. In 9 patients both the roentgenograms and the photoscans were positive. In addition, the photoscans were able to detect more extensive disease in patients with known metastatic lesions than could be shown by routine roentgenograms.

The strontium 85 photoscan is recommended as a preoperative adjunct in the over-all evaluation of patients who are potentially curable candidates by radical total prostatectomy. It is also useful in following patients during therapy of metastatic prostatic carcinoma.—*George W. Chamberlin, M.D.*

Uchiyama, Guio, Hitchcock, A. A. C., an[d] Morris, A. C., Jr. Clinical results with [a] color-recording rescanner. *J. Nuclear Med.* June, 1967, *8*, 437–443. (From: The Medica[l] Division, Oak Ridge Institute of Nuclea[r] Studies, Oak Ridge, Tenn. 37830.)

In order to observe small differences in the dis[tribution] of radioisotope in scanning techniques th[e] authors mention two methods: rescanning techniqu[e] reported by C. C. Harris and recording primary scan in color.

They state that combination of the color recordin[g] method with the rescanning technique provide[s] special usefulness, such as avoidance of necessar[y] adjustment when the patient is under the scanner better showing of the small difference in countin[g] rate, smoothing of the statistical raggedness o[f] original record, modification of the original light o[r] dark photoscan for better readability and manipula[tion] of the data without damaging the origina[l] stored data.

Several clinical examples of color rescanning wit[h] a rescanner with color read-out are presented an[d] discussed.—*A. M. Rejali, M.D.*

Ben-Porath, Moshe, Clayton, Glenn, and Kaplan, Ervin. Modification of a multi-isotope color scanner for multi-purpose scanning. *J. Nuclear Med.*, June, 1967, *8*, 411–425. (From: Radioisotope Service, Veterans Administration Hospital, Loyola University Stritch School of Medicine, Hines, Illinois, and the University of Illinois College of Medicine, Chicago, Ill.)

A technique using dual pulse height analyzer count rate system has been used by the authors for electronic subtraction of one gamma photopeak from another. This allows subtraction of Au^{198} photopeak from Se^{75} photopeak in pancreatic scanning using colloidal gold (Au^{198}) and Se^{75} tagged selenomethionine, and permits elimination of the liver scan from the pancreatic scan.

Using similar circuitry, a commercially available color scanner has been converted into a multi-isotope scanner which can simultaneously scan two isotopes emitting gamma photons of different energy levels and display on the recording paper the distribution of each isotope either in positive or negative modes or combination of both in different colors. The overlying part can be displayed in intermediate color or shades of two colors.

Combination of two colors and substract circuits to the color scanner make it possible to scan up to three isotopes simultaneously.

Various clinical applications of two and three isotope scanning by this method are demonstrated by the authors.—*A. M. Rejali, M.D.*

CHEMOTHERAPY

Hardisty, R. M., and Norman, Patricia M. Meningeal leukaemia. *Arch. Dis. Childhood*, Aug., 1967, *42*, 441-447. (From: The Department of Haematology, Institute of Child Health, The Hospital for Sick Children, Great Ormond Street, London W. C. 1, England.)

Of 131 cases of acute leukemia seen at The Hospital for Sick Children from January 1, 1958 to February 28, 1966, 29 have developed manifestations of meningeal infiltration. Fifty episodes have occurred in these 29 children and are the basis for the present report.

The most common presenting symptoms were those of increased intracranial pressure. The "hypothalamic syndrome" (rapid weight gain associated with voracious appetite) was seen in one-half the patients. Twenty-four were considered to be in hematologic remission and 26 were in relapse at the time of their episodes. The total cell count was elevated in every case in which the cerebrospinal fluid was examined (48 of 50 times). Extremely high cell counts seemed to carry a worse prognosis.

Forty-two episodes were treated with intrathecal methotrexate, 4 with radiotherapy, 2 with steroids alone, and 2 were untreated. All those treated with methotrexate responded but recurrence has been seen to date in over one-half of the cases. The authors favor this latter method of therapy.

When the over-all survival times were compared with an equal number of similar cases in which no meningeal involvement was found a statistical difference was not apparent. Meningeal involvement does indicate an advanced stage of the leukemic process however, since it is most often seen toward the end of the course of the disease process.—*Howard West, M.D.*

Mackenzie, A. Ranald, Duruman, Nevzat, and Whitmore, Willet F., Jr. Mithramycin in metastatic urogenital cancer. *J. Urol.*, July, 1967, *98*, 116-119. (From: Department of Surgery, Urology Service, Memorial Hospital, New York, N. Y.)

Mithramycin is an antitumor antibiotic, acidic in reaction, and bright yellow in color. It is readily soluble in water. It exhibits marked activity against gram positive bacteria and certain types of malignant tumors. It is a potent inhibitor of ribonucleic acid synthesis and in this respect it resembles actinomycin D but its potency is only one-tenth that of actinomycin D.

The authors have used mithramycin in the treatment of 17 patients with metastatic cancer. This was given intravenously in doses of 25 to 50 μg. per kg. body weight daily for 3 to 10 days. In 3 of 6 patients with metastatic cancer of the prostate a reduction in pain was noted during the treatment and for several days thereafter. There was no measurable evidence of regression of tumor and the serum acid phosphatase was not affected. Toxic effects were noted in 4 patients, 1 of whom died of throbocytopenia, uremia and hypocalcemia.

Of 9 patients with metastatic testicular cancer, 4 noted a reduction in pain. Three showed partial regression of metastases. Six of this group experienced nausea and vomiting without thrombocytopenia. There was no substantial clinical improvement in any of the patients. Two patients with retroperitoneal rhabdomyosarcoma and 1 with renal cell carcinoma failed to derive any benefit.

The authors conclude that mithramycin is an effective agent in the treatment of metastatic cancer of the testicle and may at times succeed in eliminating all evidence of disease. Its toxicity is less predictable and it is less effective than actinomycin D which is preferred in the treatment of embryonal cell carcinoma, teratocarcinoma and choriocarcinoma.—*George W. Chamberlin, M.D.*

Houttuin, Erik, Van Prohaska, John, and Taxman, Phillip. Response of male mammary carcinoma metastases to bilateral adrenalectomy. *Surg., Gynec. & Obst.*, Aug., 1967, *125*, 279-283. (From: The Department of Surgery, University of Chicago, Chicago, Ill.)

In an effort to assess the response to adrenalectomy in male breast carcinoma the authors studied 23 such cases seen from July 1935 to June 1960. Twelve of these patients had distant metastases and underwent various forms of endocrine ablative surgery. Six of the 12 underwent orchiectomy and sequential adrenalectomy.

Objective response, defined as disappearance of pulmonary or skeletal metastases for a period of at least 6 months was observed in 70 per cent of those undergoing some form of ablation. Four of the 6 patients who underwent adrenalectomy showed responses varying from 1 to 5 years. Two of these cases are discussed in detail.

The authors feel that endocrine ablation is the most effective form of therapy in metastases from this disease.—*Howard West, M.D.*

Anderson, E. Everett, Cobb, Oliver E., and Glenn, James F. Cyclophosphamide hemorrhagic cystitis. *J. Urol.*, May, 1967, *97*, 857-858. (From: Department of Surgery, Division of Urology, Duke University Medical Center and Duke University School of Medicine, Durham, N. C.)

Cyclophosphamide has been rather extensively used in the treatment of neoplasms of the lymphatic

group and also for tumors of the breast and ovary. The drug may be administered by mouth or intravenously. The side reactions are nausea, vomiting, diarrhea, vertigo, hepatitis, leukopenia, alopecia and cystitis.

The authors report 2 cases, one an 8 year old boy and one a 27 year old man, who developed cystitis following the administration of this drug. In one instance the hematuria and bladder symptoms subsided promptly after discontinuing the drug. In the other instance the patient continued to have severe hemorrhagic cystitis after withdrawal of the drug and it was necessary to bypass the bladder by ileal conduit. The bladder symptoms subsided promptly after urinary diversion.

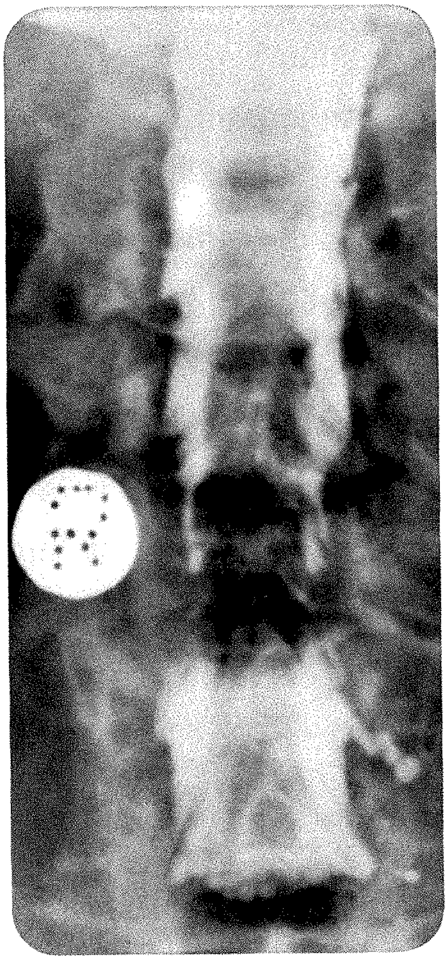
In the instances of cytoxan cystitis the urine is usually sterile. Cystoscopy reveals a hemorrhagic edematous bladder of varying degrees of severity. In the milder cases this may subside in a few days after cessation of the drug, but it may persist for 2 months after discontinuance of the drug. Prolonged administration may produce chronic fibrosing cystitis, with exsanguinating hemorrhage.

This type of cystitis can be produced in normal dogs by infusing their bladders with urine obtained from dogs which had developed cyclophosphamide cystitis from massive intravenous infusions of the drug. The resulting hemorrhagic cystitis was indistinguishable from that of the donor dogs. Cyclophosphamide *per se* infused into the bladders of normal dogs did not produce this same picture. Therefore, it is assumed that cytotoxic effects on the bladder are due to urinary metabolites of cyclophosphamide rather than to the drug itself or to its systemic effects. Further animal experiments indicate that forced hydration and diuresis may be helpful in preventing this syndrome.—*George W. Chamberlin, M.D.*

Phelan, John T., and Milgrom, Halina. The use of the Mohs' chemosurgery technique in the treatment of skin cancers. *Surg., Gynec. & Obst.*, Sept., 1967, *125*, 549–560. (From: Department of Surgery and Dermatology, Roswell Park Memorial Institute, New York State Department of Health, Buffalo, N. Y.)

The authors report on 446 consecutive skin cancers treated by Mohs' chemosurgery technique. Nonmetastasizing basal cell carcinoma accounted for over 80 per cent of the lesions.

Of the cancers treated by this method, those with ill-defined borders and those complicated by infection and scarring were the most suitable. The technique was also of value in the management of multiple lesions of the face and of recurrent lesions involving the alar base region of the nose, the scalp, and the ears.—*Richard P. Taylor, M.D.*



Progressive bilateral numbness, weakness, and muscle atrophy that had been present for one year in a 57-year-old man was attributed to cervical spondylosis. A myelogram using 12 cc of PANTOPAQUE [Iophendylate Injection] demonstrated the large defect at the level of the fifth cervical vertebra. The patient recovered rapidly following laminectomy and posterior decompression of the fifth cervical spinal nerve roots.

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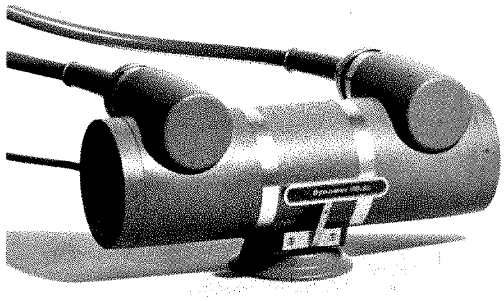

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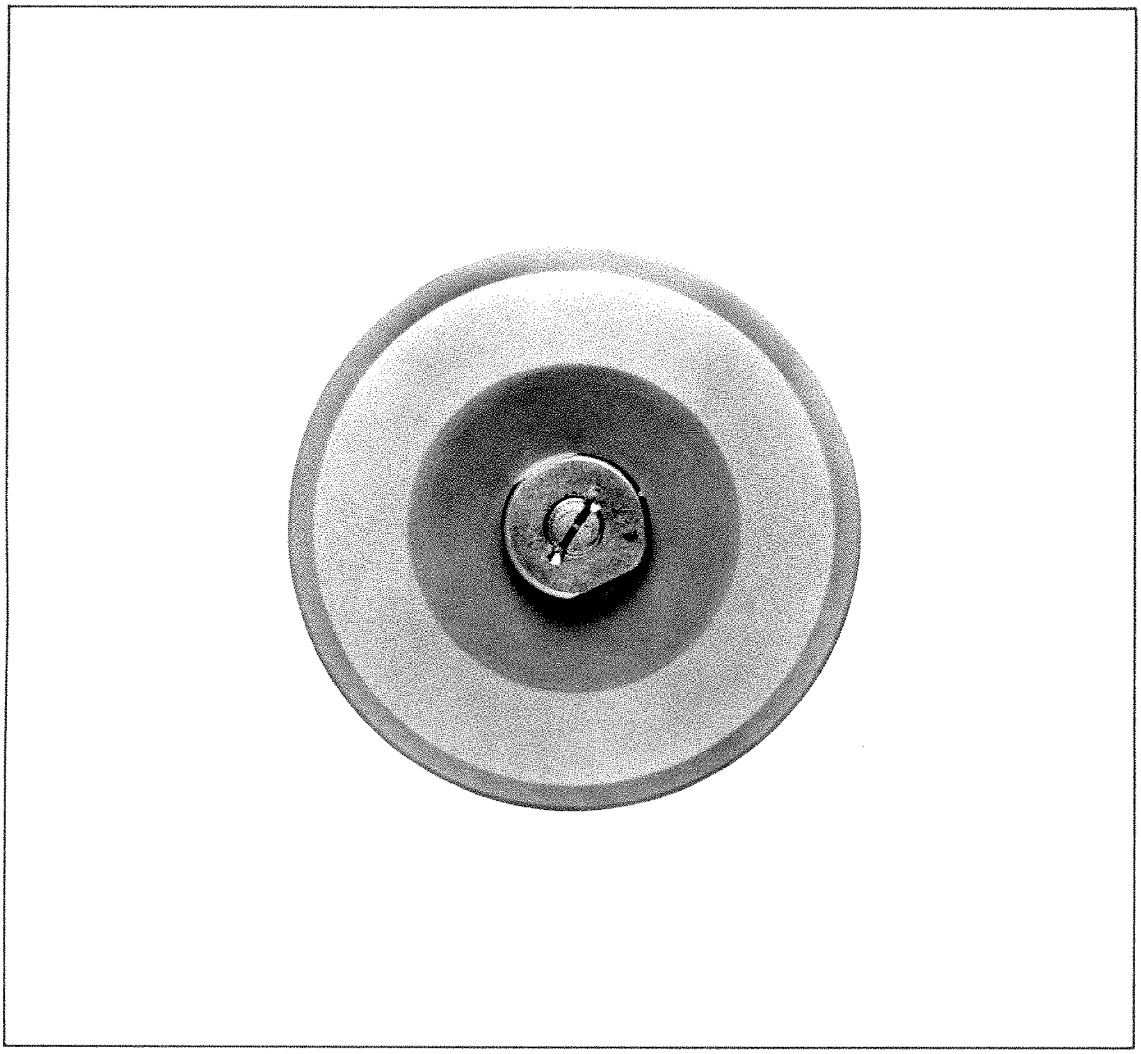

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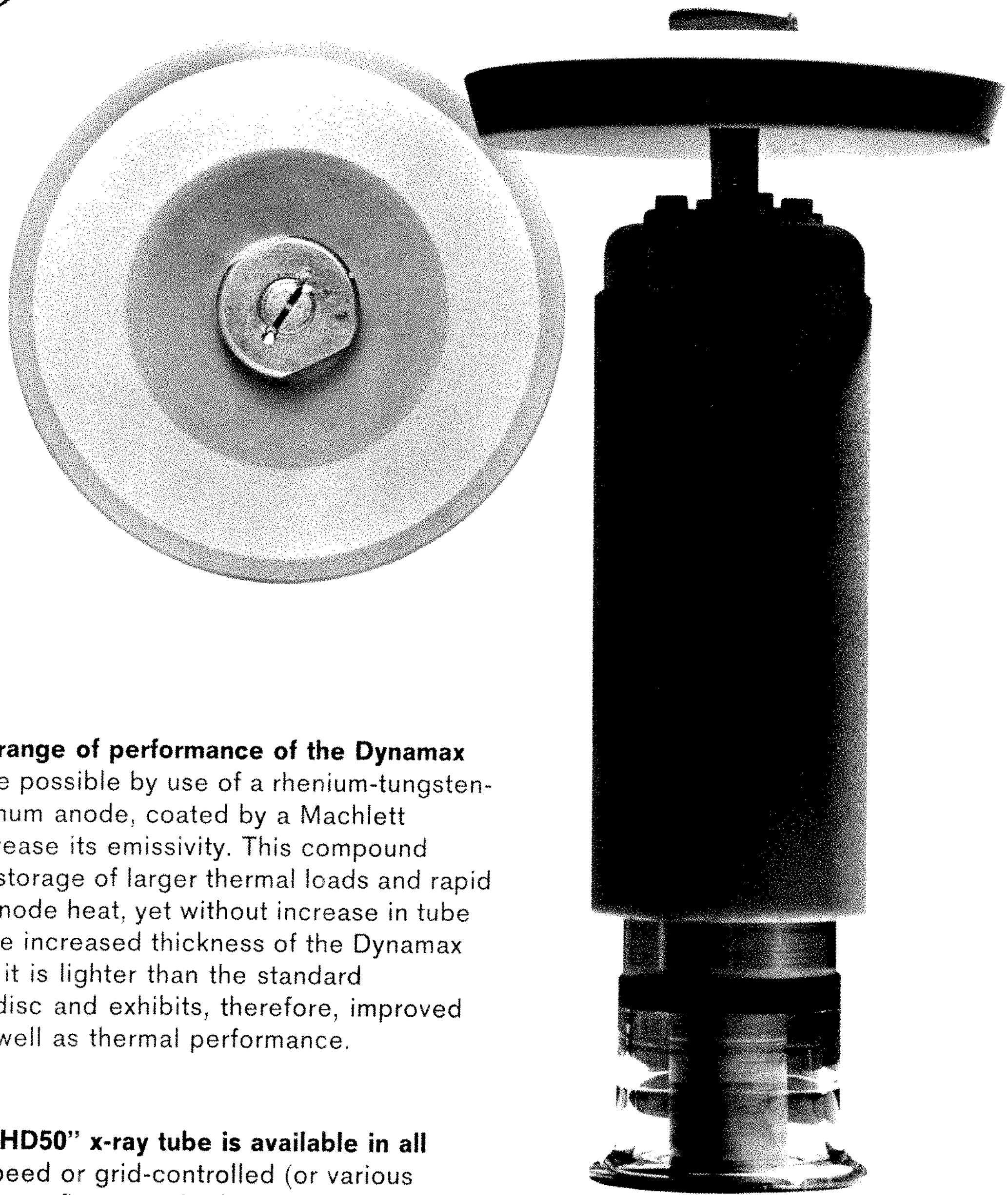

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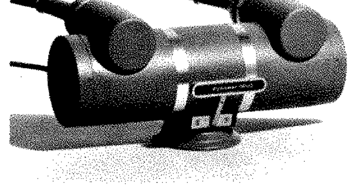
For details on the Dynamax "HD50" rotating anode x-ray tube, write: The Machlett Laboratories, Inc., Springdale, Connecticut 06879.



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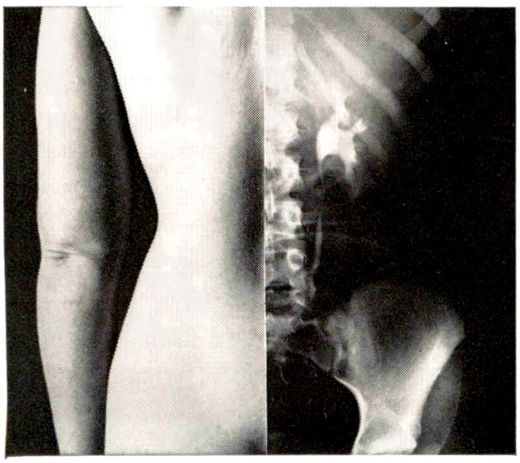
Renografin-60 (meglumine diatrizoate injection) preferred in a study of pyelographies of 2,234 patients.

In a new large scale study,[1] "...to determine which medium would produce adequate visualization of the urinary tract with the fewest toxic effects on the patient," Macht *et al.* have compared Renografin-60 with 2 other contrast agents.

Data were analyzed in 2,234 unselected (consecutive) patients, according to age, sex, and general disease group for the study population as a whole. The first 683 patients received 50% diatrizoate sodium solution, the next 921 patients received Renografin-60, and the final 630 patients received 66.8% sodium iothalamate solution.[1]

criteria for quality and comparative safety The contrast agents were evaluated for quality of diagnostic films as follows: films showing a dense concentration of contrast medium with filling and visualization of all major and minor calyces, infundibula, pelves and almost all of each ureter were listed as "good"; films showing less concentration with incomplete visualization of all portions of urinary tract but sufficient to produce diagnostically adequate films were listed as "fair"; films showing unsatisfactory visualization of urinary tract, or films which could not be interpreted, as "poor." The media were also evaluated as to incidence of the following side effects: nausea, vomiting, fainting, shock or severe reaction, hiccups, hives, pain in arm, sneezing, hot flushes, stuffiness of nose or ears.[1]



The following chart* shows comparative results of the 3 media according to age category:

quality of pyelograms and side effects expected in standard population of 1,000 patients by age, according to type of medium used

medium used and type of patient	standard population	quality of pyelograms good	fair	poor	with side effects
meglumine diatrizoate					
all ages,	1,000	827	123	50	41
0-19†	126	122	3	1	3
20-49	415	374	35	6	27
50-69	315	240	51	24	9
70 or older	144	91	34	19	2
diatrizoate sodium					
all ages,	1,000	782	134	84	72
0-19	126	115	6	5	7
20-49	415	378	26	11	40
50-69	315	227	64	24	19
70 or older	144	62	38	44	6
sodium iothalamate					
all ages,	1,000	883	81	36	54
0-19	126	122	4	0	7
20-49	415	393	20	2	29
50-69	315	269	32	14	13
70 or older	144	99	25	20	5

*Adapted from Macht[1] †In some patients in this age group, higher than recommended doses were used.

In theory: "The choice of contrast agent should ideally be individualized according to the age, sex, and disease group of the patient in order to obtain a high probability of complete visualization of the urinary tract with low probability of adverse side effects."[1]

In practice: "The choice is to be made...on the basis of the agent which gives the best concentration and the fewest side effects in the greatest number of patients regardless of age, sex, or disease category."[1]

In order of preference: Although Renografin-60 was not rated highest in all categories, the authors feel that their preference of the contrast media for intravenous pyelography would be: first, Renografin-60; second, sodium iothalamate; third, diatrizoate sodium.[1]

For brief summary of prescribing information, please refer to the end of this advertisement.

definition of safety...

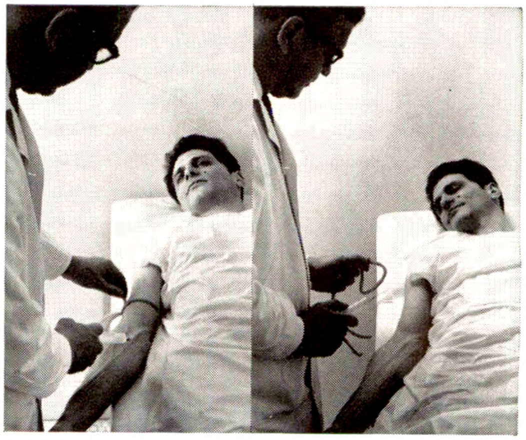
demonstrated in animals... Since meglumine diatrizoate is also used for cerebral angiography, toxicity studies of administration via the carotid artery are therefore of interest. Fischer and Eckstein[2] designed angiographic studies in animals in which procedures were very similar to clinical angiography, and which yielded data that was quantitative, graphic and nonsubjective.[2] According to the authors: "We selected the alterations in arterial blood pressure, venous pressure, heart rate and rhythm, the electrocardiogram and end-expiratory CO_2 concentration resulting from experimental cerebral angiography as refined, sensitive indications of the toxicity of a particular contrast material."[2] Their results of measured cardiovascular functions in dogs indicated that meglumine diatrizoate was far less toxic than four other contrast media.[2] As Fischer and Cornell reported in a later study: "Despite the testing of more highly concentrated solutions and larger doses, the cardiovascular responses [in dogs] from methylglucamine [meglumine] salts were much less than from sodium salts, an observation consistent with previous experiments."[3]

Other investigators have documented the comparative safety of meglumine salts in experimental studies. In order to determine reaction and tolerance of the intestines, Cooley[4] injected meglumine diatrizoate into mesenteric arteries of dogs and found no damage. Gensini *et al.*[5] reported that cardiovascular responses with it were almost identical to blood transfusions.

theory of lower toxicity with meglumine... Gensini and DiGiorgi have offered a hypothesis to explain their findings of lesser toxicity with experimental intravascular injections of methylglucamine (meglumine) salts. "When a relatively undiluted amount of sodium salts of a contrast agent is injected in an artery and carried by the blood stream toward the capillary bed, its molecules rapidly dissociate and readily diffuse through the capillary membrane and into the tissue. There, both the toxic effect of the iodine-containing organic radical and the increased concentration of sodium will readily manifest themselves. At equal concentrations of sodium, the end results will closely reflect the intrinsic toxicity of the iodine-containing organic radical on the tissues...."[5]

"In the case of the methylglucamine compounds, the same dissociation takes place. However the larger methylglucamine molecule, rich in hydrogen bonds, apparently either limits the migration of the organic radicals outside the vessel or at least minimizes their effects on the cellular metabolism."[5]

proved in practice... Paralleling similar findings in animals, clinicians have reported a generally lower



incidence of untoward reactions with Renografin-60 in urologic and cerebrovascular use. However, as with all intravascularly injected contrast agents, the possibility of severe reactions should be kept in mind (see Contraindications, Precautions and Side Effects below). In one study of over 600 urologic patients, the investigators reported that Renografin-60 produced urograms of diagnostic quality with a 6% incidence of side effects. The authors concluded: "It is hard to believe that any drug introduced intravenously could be so well borne by so many patients...."[6]

In a 74-patient study,[7] comparing Renografin-60 with diatrizoate sodium in carotid arteriography, Shealy commented: "With confused patients who are to have arteriography under local anesthesia, it is particularly desirable to have an agent that causes little pain." In this study, since "...60 per cent Renografin has resulted in considerably less pain than 50 per cent or 45 per cent [diatrizoate sodium]...we have converted to the routine use of 60 per cent Renografin for carotid arteriography; an additional 1,500 arteriograms done with 60 per cent Renografin have been quite satisfactory."[7]

better tolerated even in pediatrics... Citing some difficulties in administering contrast agents intravenously to children, Strasser *et al.*[8] selected Renografin-60 for intramuscular use in excretion urography in 16 pediatric patients because of the mild and relatively few reactions consistently associated with its use. The authors concluded: "The almost complete absence of any kind of local effect from its injection into the gluteal muscle and the absence of any serious reactions, local or systemic, indicate the safety of the medium."[8]

For brief summary of prescribing information please refer to the end of this advertisement.

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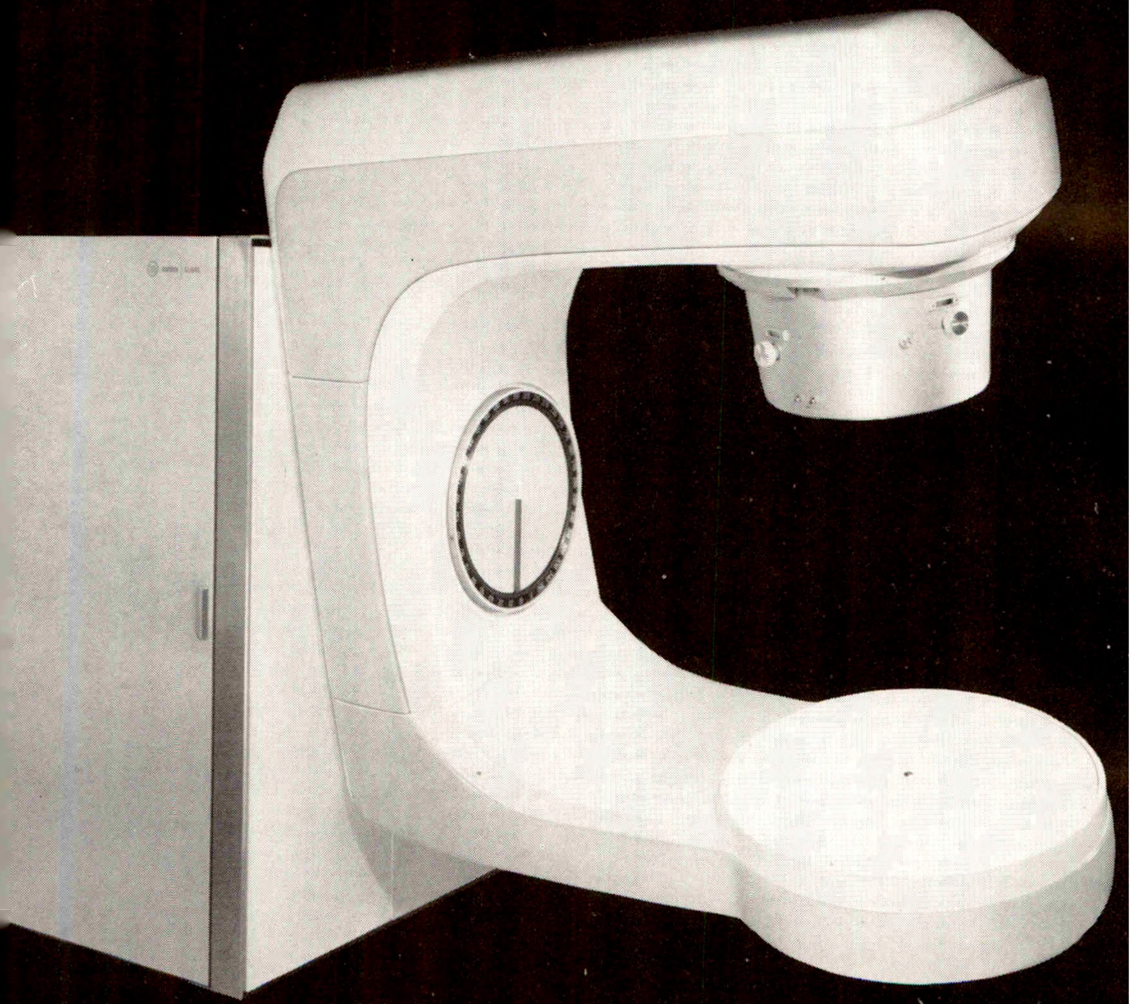

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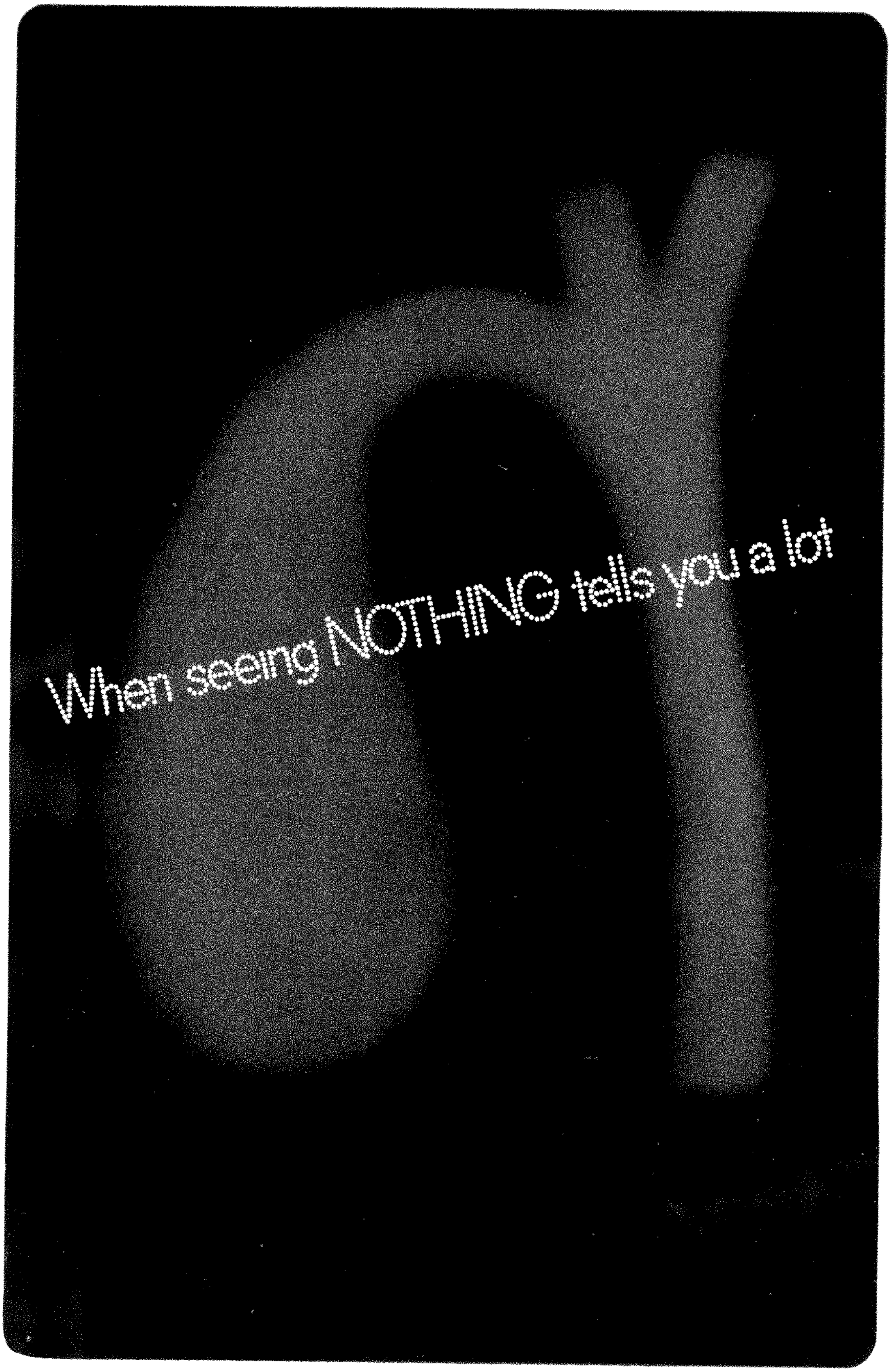
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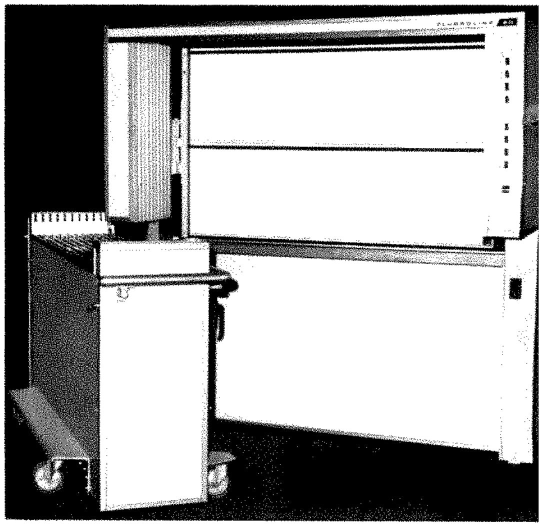

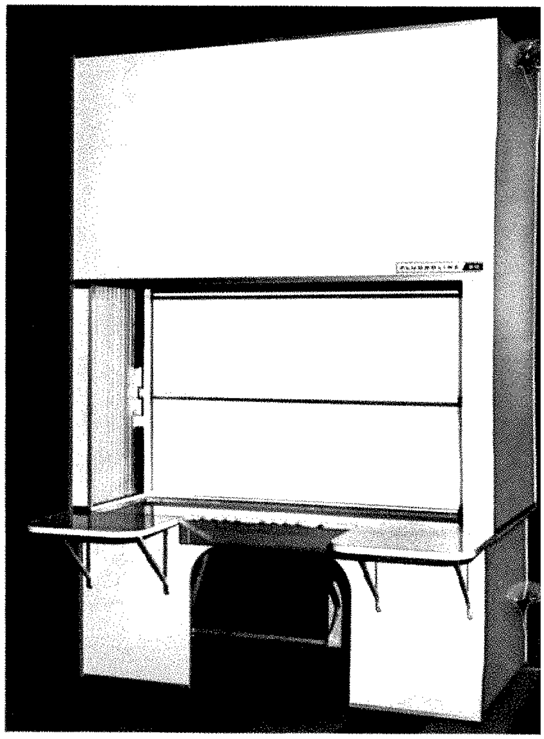

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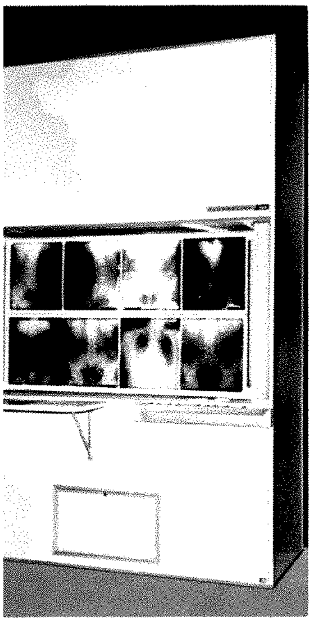

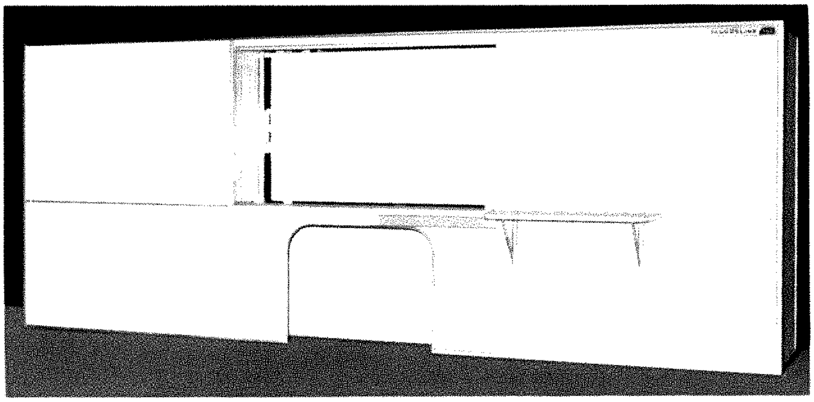

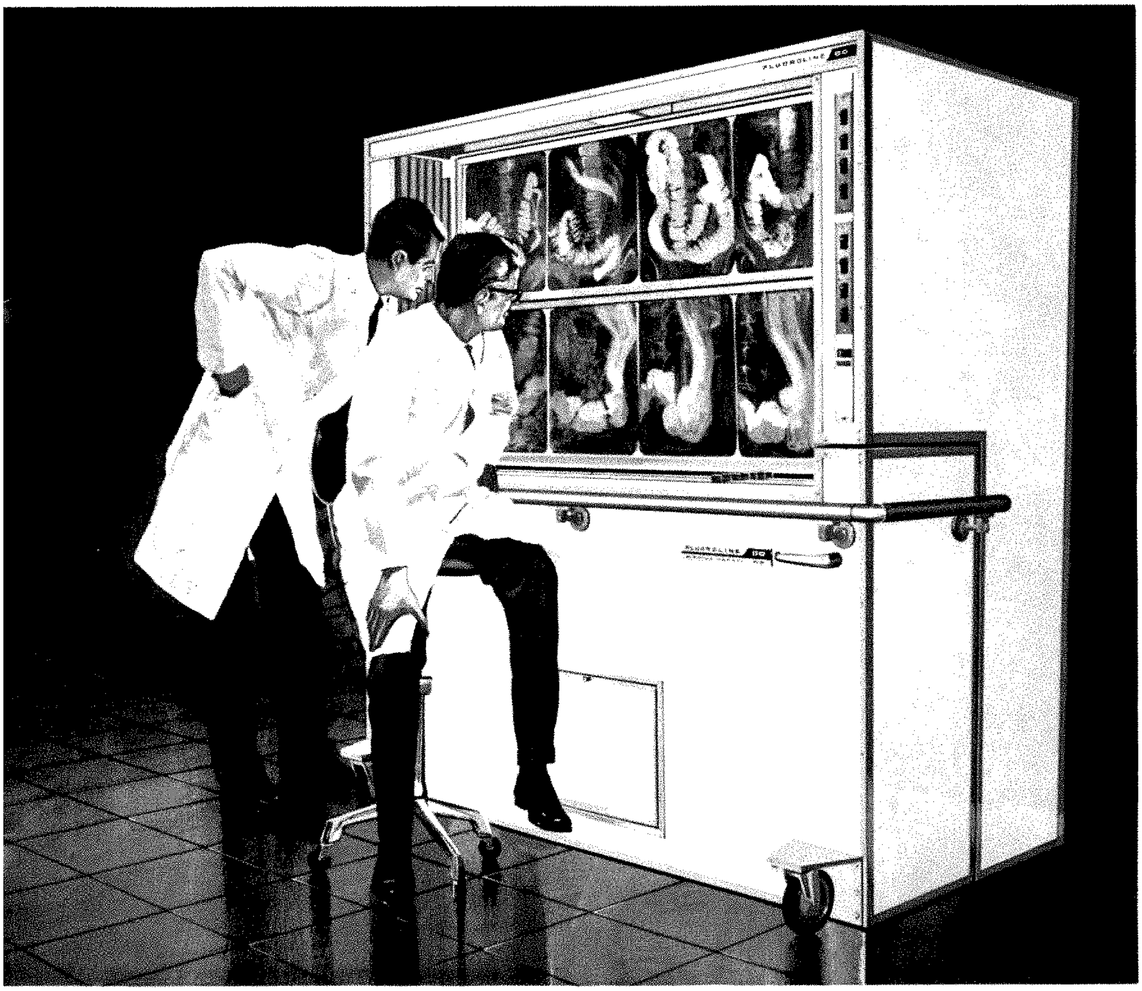

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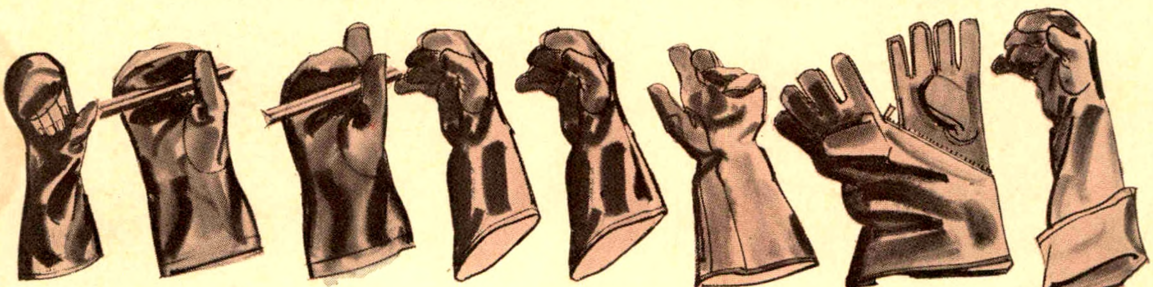

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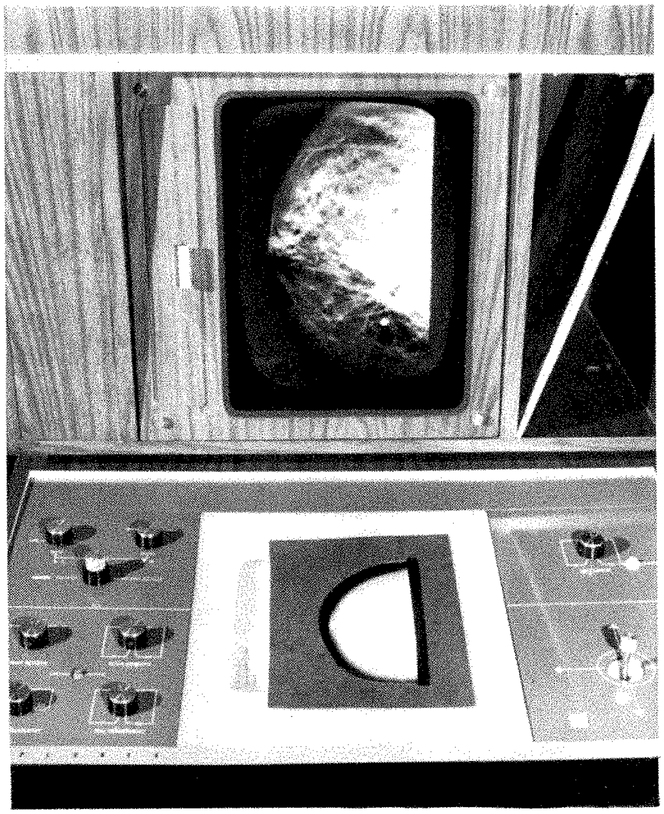

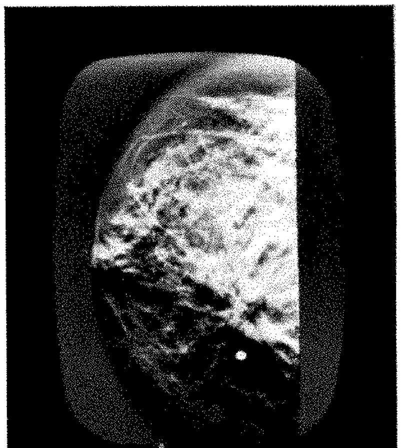

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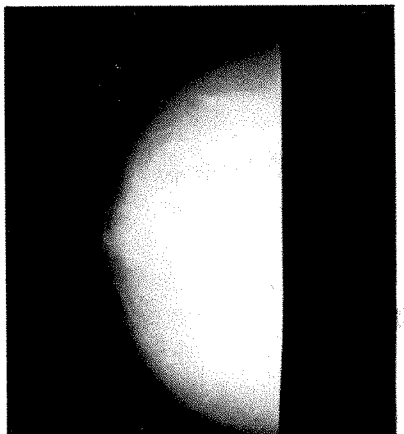

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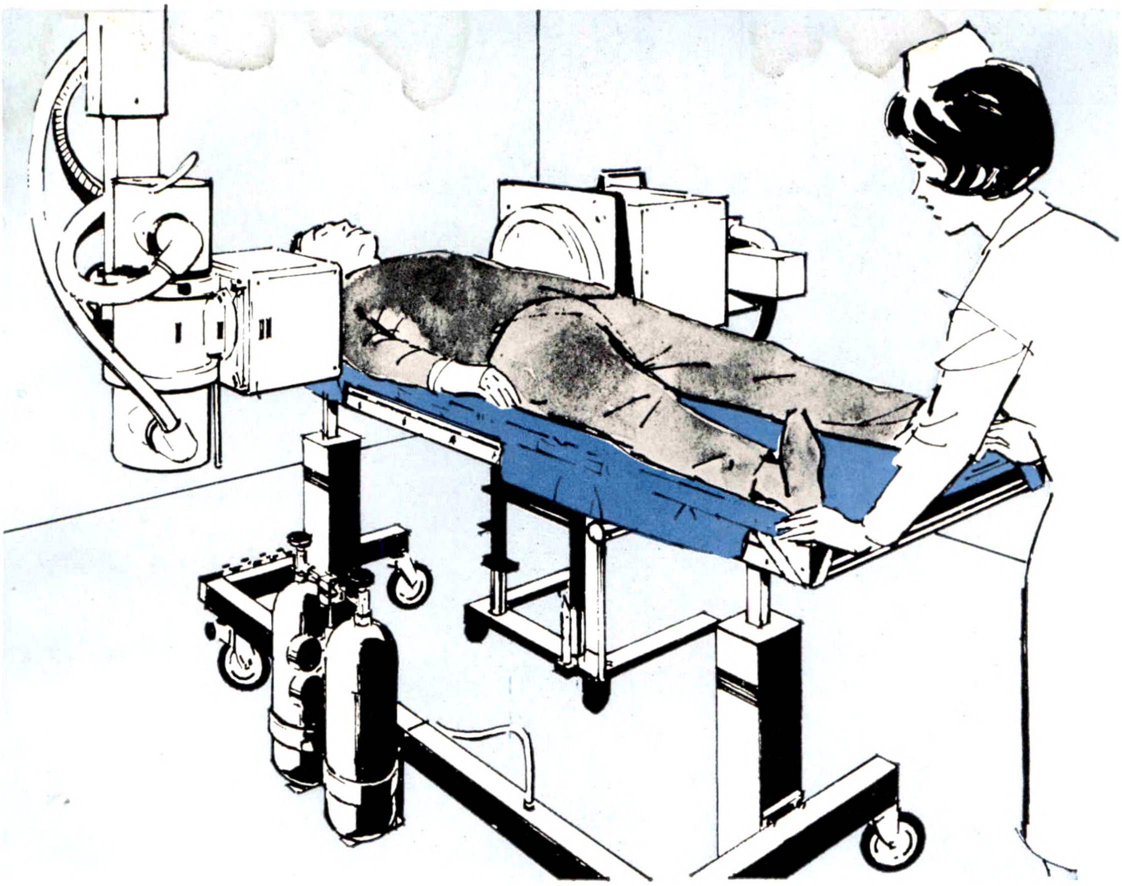
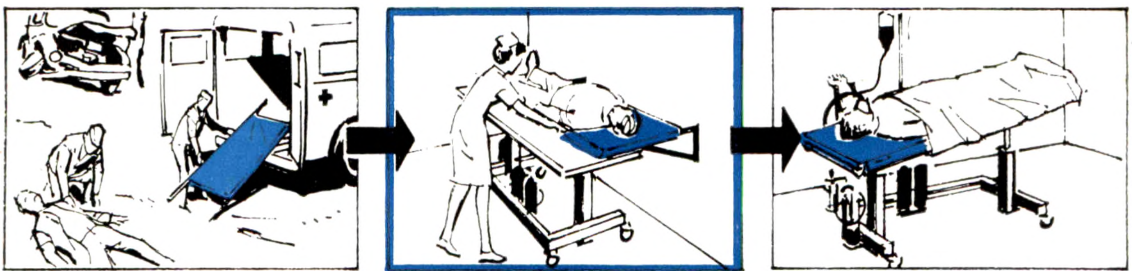
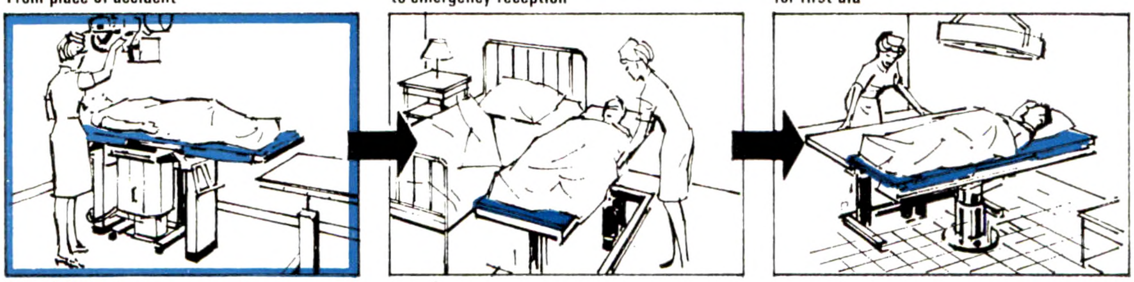


CASUALTIES - transport and care



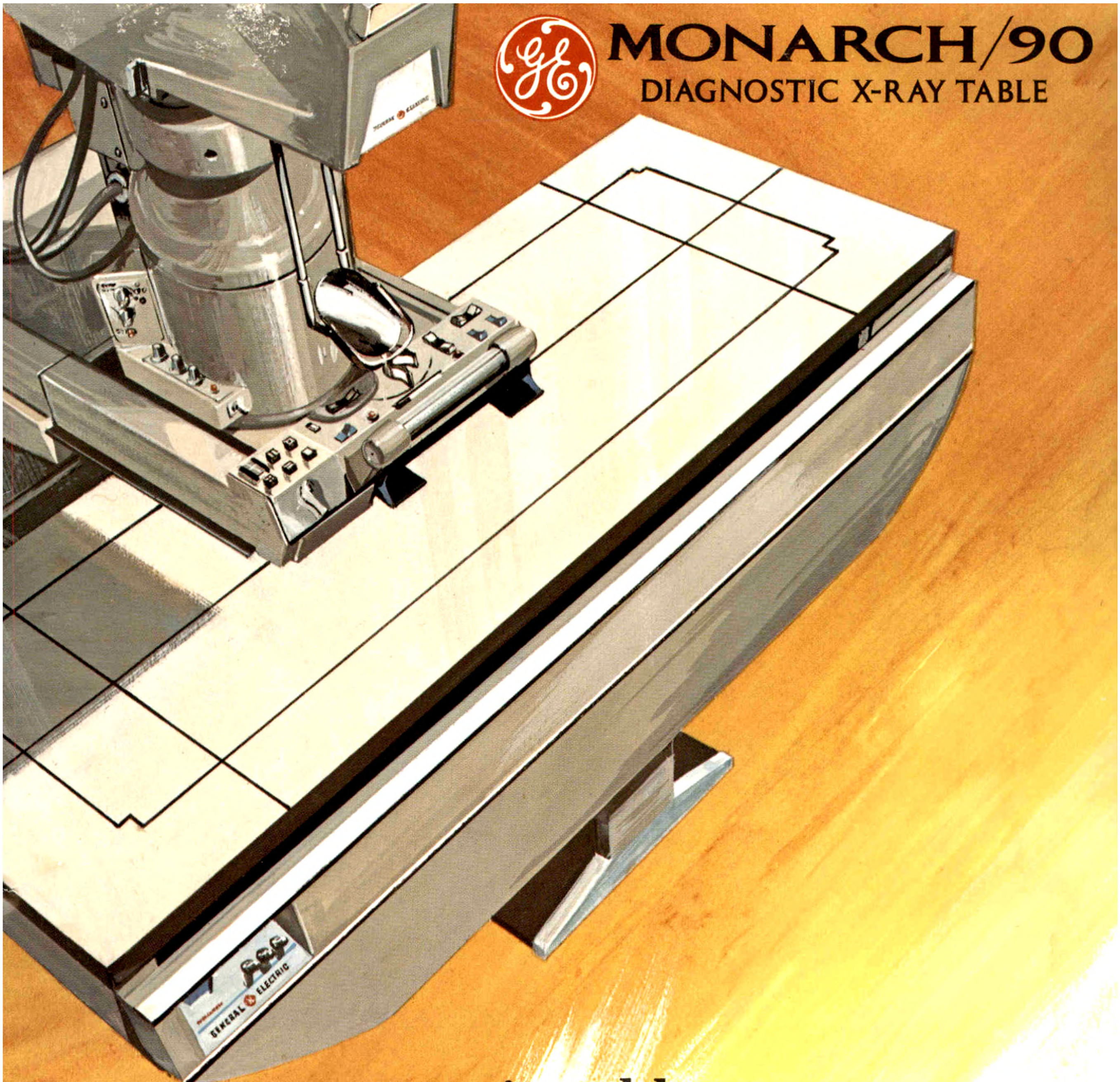
From place of accident — to emergency reception — for first aid



through X-ray department — to bed — or operation

→ on the same mattress

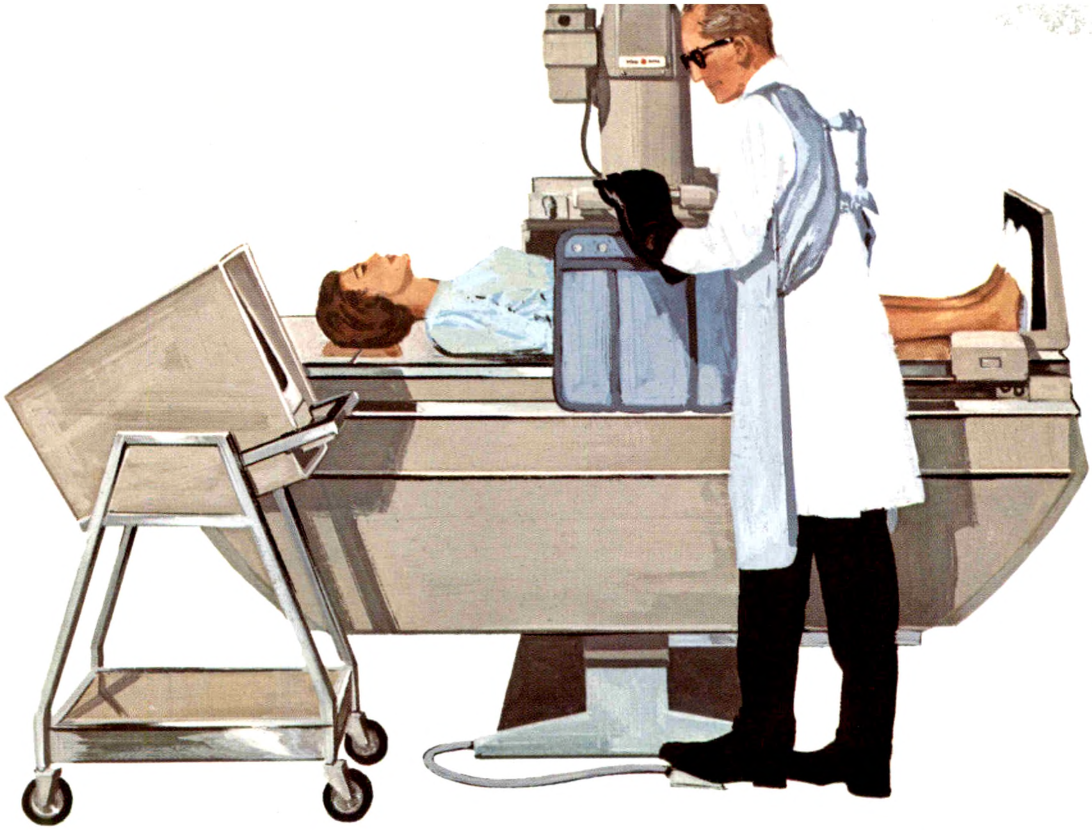
MONARCH/90
DIAGNOSTIC X-RAY TABLE



...tops in tables

For routine examinations or special procedures, the sturdy Monarch/90 is truly "tops" in any installation. This is the table that is built for ease of operation and for patient comfort. All controls are positioned for fast accessibility. Time-consuming coupling, parking and uncoupling of equipment is virtually eliminated. The Monarch/90 features powered 90-90 degree angulation and table-top movement at a touch and can be equipped with a wide variety of supplementary devices. When you order a Monarch, you choose the spot-film device, image intensifier, tube support and patient safety and comfort features to meet your requirements. Check out a Monarch table soon. It's the finest table made for every fluoroscopic and radiographic requirement.

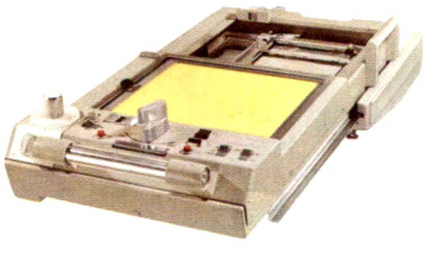
Interested in Consistent Results? Turn Page...

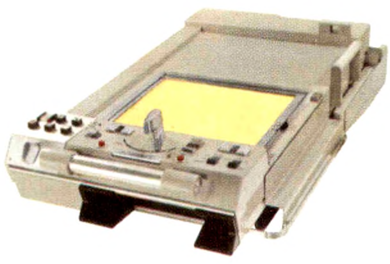


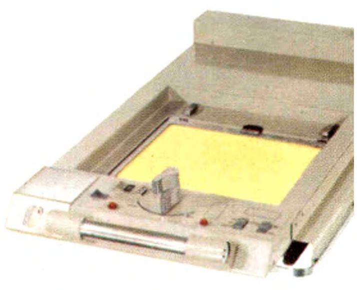
MONARCH/90

Servo-Controlled True Field Collimation

Improved quality spot-film and fluoroscopic image is provided by electric servo-controlled GE True Field Collimator, now built into the Monarch/90. It allows for multiple levels of collimation, resulting in an absolute minimum of off-focal-spot radiation. Servo control assures a definite visual relationship between control handle positions and collimator blade positions Fluoroscopic exposure area remains constant even as the spot-film device is moved towarc or away from the patient. The Monarch accepts a choice of top-loading or end-loading spot-film devices, or a Fluoricon Pedestal when a cassette facility is not desired.







Model 8 Top-Loading Spot-Film Device features fully-powered cassette transfer, automatic dial sequencing and optional two-speed power assist; servo-collimator is manually controlled; especially designed for easy loading of 8 x 10 cassettes from front or rear of table.

Model 9 End-Loading Spot-Film Device features push-button sequence selection—1 on 1, 2 on 1 horizontal, 2 on 1 vertical and 4 on 1. Choice of manual or automatic fluoroscopic beam control; automatic collimation consistent with exposure pattern selection—manual collimation determined by position of control handles. End-loading design provides fast, simple 9½ x 9½ cassette changing.

Model 10 Fluoricon Pedestal c
any one of three different requ
—as a support for a Fluoricon
and camera with no external su
attachment device for all Fluoric
external support; or as a fluc
screen unit.

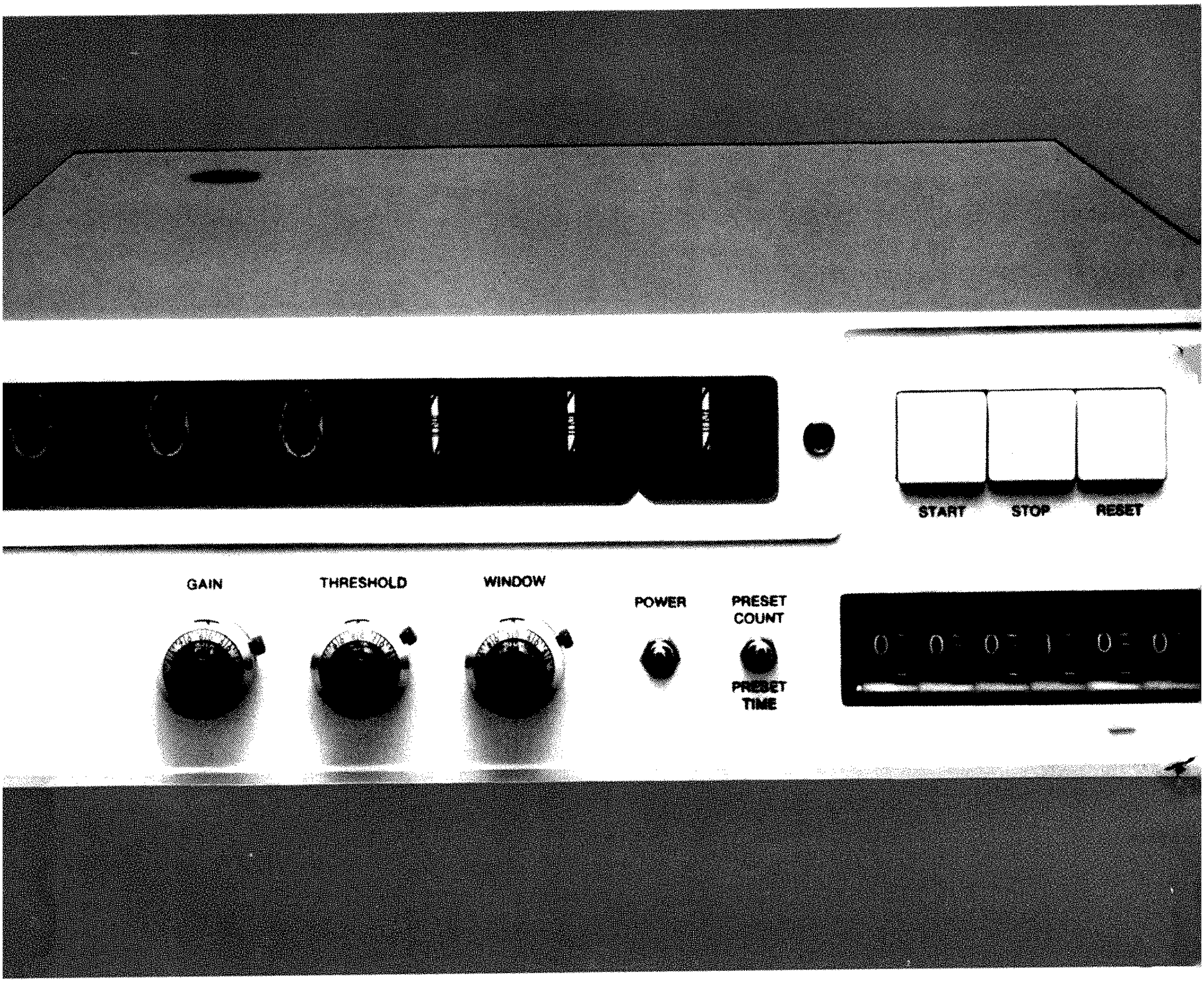
Progress is our most important product

GENERAL ELECTRIC

1704

Printed i

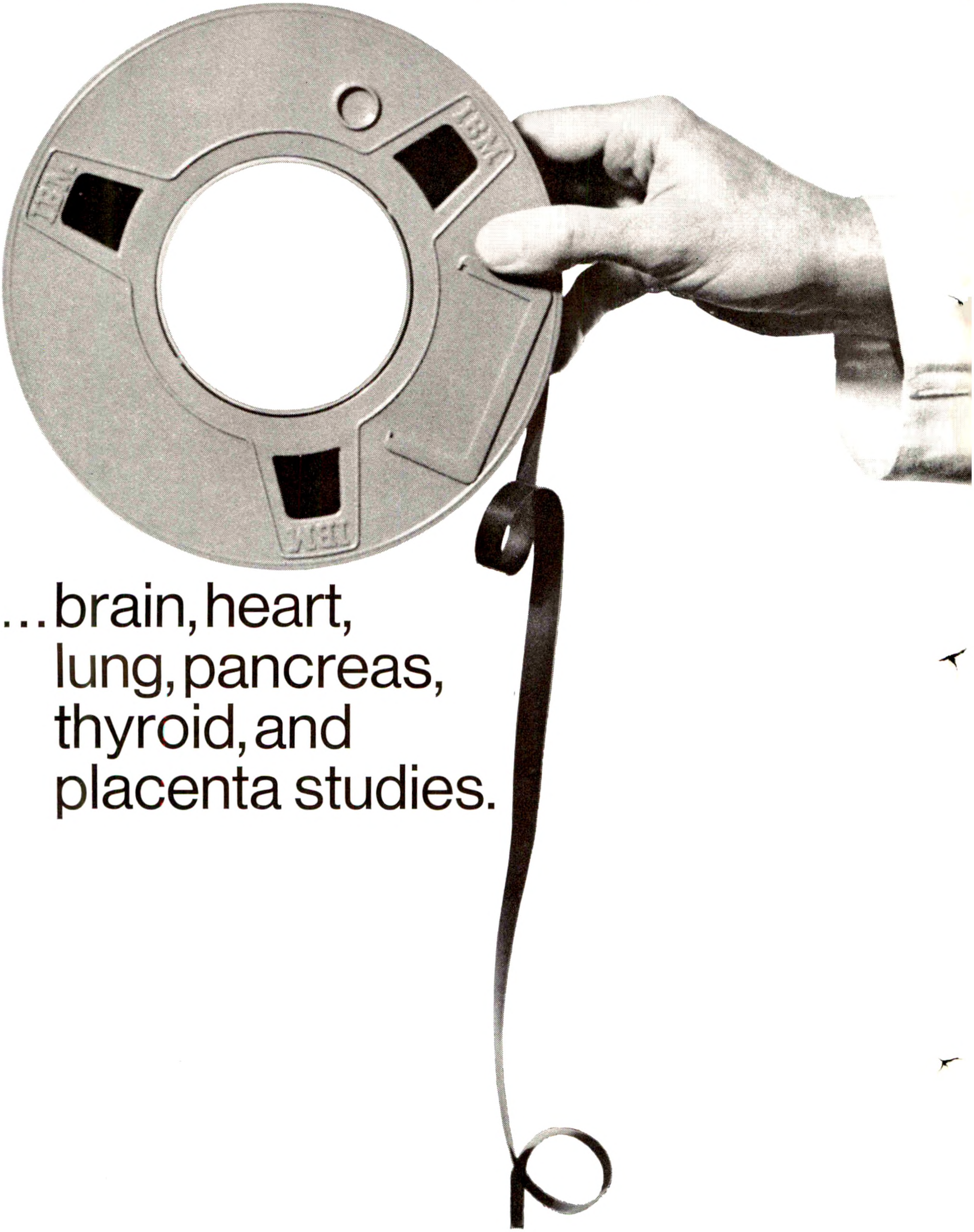
Abbott Laboratories is now



This is the
LOGIC™ Well Counter–
only inches larger than this page
(12¼" x 4$\frac{1}{16}$" x 13" to be exact)

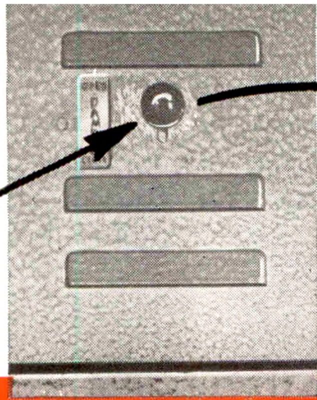
TM—TRADEMARK

You are now looking at 1200 feet of liver, kidney ...



... brain, heart, lung, pancreas, thyroid, and placenta studies.

What's so special about Halsey Film Dryers?...



The climate compensator control!

Model No. 601-D

Model No. 600-D

It solves the humidity problem!

The biggest bugaboo of film dryers is humidity in the darkroom . . . environmental moisture which turns the most efficient unit into a sluggish, slow-acting flop.

Now HALSEY introduces the *climate compensator* – a system of air control that lets you shut out outside humidity when it's too high . . . or bring in outside air when it's cool and dry.

The result . . . faster film drying – regardless of climate conditions!

No. 600-D. Fatigue-free loading from the top. Handles 12 films every 20 minutes. Complete with automatic timer — a guard against fire hazard due to failure to turn off the heater. Dimensions: 23″ wide, 33″ high, 17½″ deep.

No. 601-D. Economy version of above — loads from the front. Recommended for stacking on top of No. 600-D for stoop-free loading, when extra capacity is desired. Dimensions: 23″ wide, 33″ high, 17½″ deep. Automatic Timer (No. 602-DT) available.

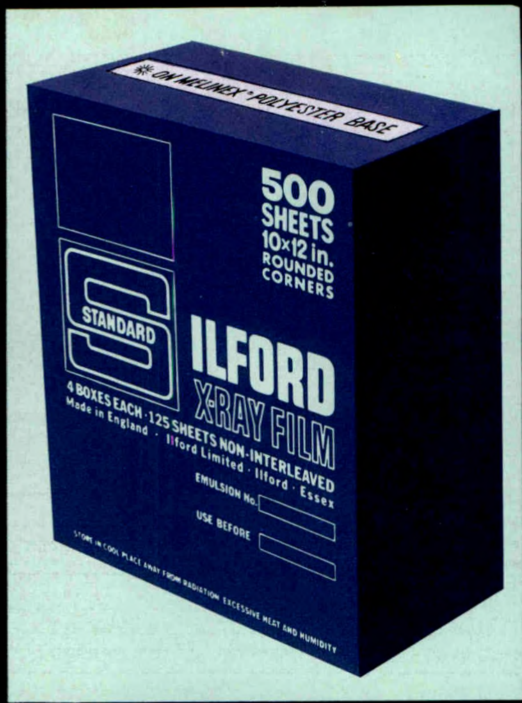
No. 601-D-H. For restricted space — similar to No. 601-D, but almost 10″ narrower; accommodates 6 films. Dimensions: 13½″ wide, 33″ high, 17½″ deep.

HALSEY

Through your dealer

HALSEY X-RAY PRODUCTS, INC.
1425-37th STREET, BROOKLYN, N.Y. 11218

CHICAGO: 7321 Monticello Avenue, Skokie, Illinois 60076
LOS ANGELES: 1816 W. 8th St., Los Angeles, Calif. 90057



Red Seal X-ray film on Melinex® polyester base

The premium Red Seal X-ray film now being supplied is made with an entirely new and highly efficient emulsion coated on Melinex polyester base and is designed to produce maximum radiographic information.

Red Seal on Melinex base is a high speed film with excellent resolving power, resulting in minimum exposures and sharp, clean images. Fog is at an absolute minimum for a film of this speed. This new Red Seal emulsion will give equal satisfaction throughout the entire medical KV range.

Standard X-ray film on Melinex® polyester base

Standard X-ray film on Melinex base, like Red Seal, is designed to produce maximum radiographic information.

This fine film offers all the qualities sought by radiologists: high contrast, medium speed, fine grain (particularly suitable for use with high KVP techniques); exceptionally low fog level, and the famous Ilford batch-to-batch and box-to-box consistency.

Standard X-ray emulsion on Melinex base is particularly recommended for all investigations where the highest contrast and definition are required.

Both Ilford Red Seal and Standard X-ray films on Melinex assure superior performance in all "full cycle" and "half cycle" processing systems. In addition, these new films permit substantial reduction in drying temperatures. Packings include 300 and 500 sheet economy bulk packs, and 75 and 25 sheet cartons in all popular sizes. We invite a trial test of their excellence.

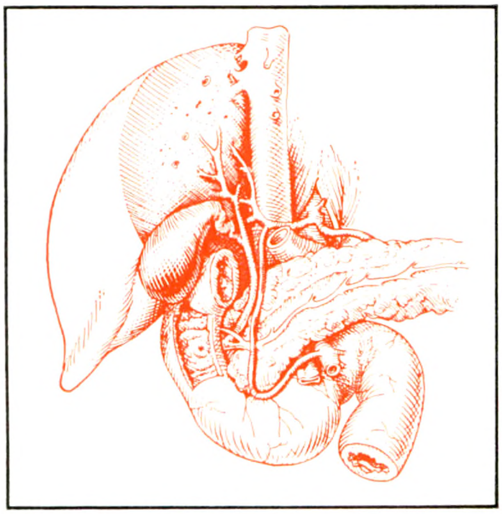
ILFORD INC.

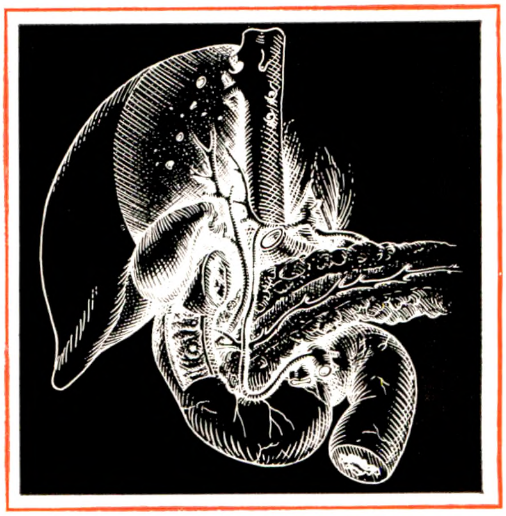
601 West 26th Street, New York, N. Y. 10001
1217 East El Segundo Boulevard, El Segundo, Cal. 90245
3566 Elm Street, Hapeville, Ga. 30054

SQUIBB

a research concept in contrast visualization

for better definition of disease: documenting differences between oral contrast agents





no. 2 in series:

Oragrafin®

Squibb Ipodate

maximum concentration with better patient toleration in oral cholangiography and cholecystography

For rapid or routine studies of the gallbladder and biliary ducts, Oragrafin provides rapid, more complete absorption, for maximum concentration and excellent contrast.

definition of maximum concentration

high absorption index—"No one will dispute the statement that the diagnostic reliability of oral cholecystography depends upon the degree of absorption of the contrast medium employed."[1] Radioisotope studies with ipodate sodium show a markedly improved absorption index (approximately 70 per cent) with no increase in the toxic properties.[1]

less bowel residue—"Incomplete and variable absorption of a cholecystographic agent is not desirable, for the opacification of the gallbladder is then less dependent on the status of the gallbladder and more a reflection of the percentage absorption."[2] "Opaque material in the bowel was found in 46 per cent of [105 patients in] the... [iopanoic acid] group as compared with 9 per cent of those [99] of the [Oragrafin Sodium Capsules]...group."[2] In another study, 49 of 100 patients receiving iopanoic acid had residue in the gastrointestinal tract, while only 15 of 100 patients receiving Oragrafin had such residue.[3]

excellent opacification—"In addition to its ease of administration and safety, its principal advantages are a high yield of diagnostic films...."[4]

definition of better toleration

low incidence of untoward reactions—In contrast to findings with other cholecystographic agents, Lewitan and Garcia[5] reported in their 246 patient study: "With

ipodate calcium...there was no clinical evidence of immediate or delayed nephrotoxicity in any of the patients given it...."[5] To study possible renal toxicity, "Creatinine clearance tests were also done before and after administration of multiple doses in excess of 6 gm. in 8 cases, and showed no significant alterations."[5] However, "Multiple doses beyond 6 gm. are not recommended."[5] In their study of 120 patients, Glenn and O'Brien reported "...no reactions in this series of patients attributable to the administration of [Oragrafin]...."[4] And, McCrory reported that Oragrafin was "...used routinely in cholecystographic studies in approximately 2000 patients with excellent diagnostic films and only rare and mild reactions."[6]

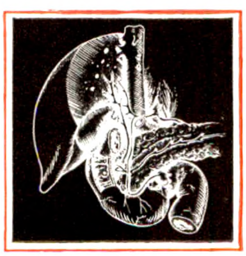
side effects compared to iopanoic acid

side effects encountered in administration of 3 Gm. of Oragrafin Sodium Capsules and 3 Gm. iopanoic acid *

	Oragrafin Sodium Capsules (Squibb Sodium Ipodate)	iopanoic acid
no. of cases	99	105
no. of side effects		
nausea		
slight	10	14
severe	2	6
vomiting	0	1
diarrhea		
mild	7	22
severe	3	16
cramps	5	15
dysuria	9	13
total/per cent	36 (36.3%)	87 (82.9%)

*Adapted from White, W. W., and Fischer, H. W.[2]

Juhl,[3] in his study of 200 patients (100 on each agent), found no significant difference between iopanoic acid and sodium ipodate in the incidence of nausea; vomiting occurred in an equal number of cases.



definition of convenience:

Oragrafin® Calcium Granules

Squibb Calcium Ipodate

visualization of poorly functioning gallbladder reduces the need for I.V. studies – In a concentrating gallbladder, Oragrafin Calcium Granules (Squibb Calcium Ipodate) will show storage, concentration, delivery or stones. A patent biliary duct can generally be expected to visualize. Provided the cystic duct is patent, Oragrafin will visualize the normal gallbladder, the abnormal gallbladder containing papillomata, nonopaque stones or radiodense calculi, and gallbladders where concentrating power is diminished.

patient convenience – Routine cholecystography night-before procedure is easy for patients to follow; palatable granules further enhance patient acceptability. Rapid clearance of medium permits same-day administration and gallbladder and ductal films, and, if necessary, same-day re-examination; reduces need for I.V. studies.

Optimal concentration in the hepatic and biliary ducts usually occurs within 1 to 3 hours. Although the gallbladder is optimally opacified 10 hours after ingestion of the agent, diagnostically valuable information can often be obtained within 5 hours or less.

rapid absorption permits same-day re-examination – To determine the cause of nonopacification after routine cholecystography, most physicians require re-examination by repeating the procedure at a later date (sometimes doubling dose), or

A 2893

by administering more agent the evening of the first unsuccessful examination (again sometimes doubling dose), and repeating the study the next day. "The advantage of the calcium ipodate method is that the examination can be completed in five additional hours with a limited dose of contrast agent."[7]

a valuable medium for peroral cholegraphy[5]—Rapidly absorbed from the gastrointestinal tract, calcium ipodate has been reported by some investigators to be diagnostically superior to other oral cholangiographic contrast agents. With careful timing of the examination and the use of tomograms or laminograms, the frequency of good results can approximate that obtained with intravenously administered agents. According to Lewitan and Garcia,[5] the medium's relative safety makes it a valuable medium for peroral cholegraphy. Timesaving and economical Oragrafin Calcium Granules may be particularly useful in certain patients for whom I.V. radiography presents potential hazards, such as elderly patients, those with cardiovascular disease, or patients who may exhibit sensitivity to the test dose of an intravenous agent.

Unique among oral media, Oragrafin Calcium Granules permits same-day films of the gallbladder and ductal system.

dosage schedule for films of gallbladder and ductal system

8 A.M.	2 packets of granules
9 A.M.	visualization of ducts
10 A.M.	optimal visualization of ducts
1 P.M.	visualization of gallbladder

References: 1. Sanen, F. J.: Amer. J. Roentgen. *88*:797 (Oct.) 1962. **2.** White, W. W., and Fischer, H. W.: Amer. J. Roentgen. *87*:745 (April) 1962. **3.** Juhl, J. H., *et al.*: Radiology *80*:87 (Jan.) 1963. **4.** Glenn, J. C., Jr., and O'Brien, P. S.: Southern Med. J. *56*:167 (Feb.) 1963. **5.** Lewitan, A., and Garcia, J. F.: Amer. J. Dig. Dis. *10*:219 (March) 1965. **6.** McCrory, E.: J. Tenn. Med. Ass. *58*:258 (Aug.) 1965. **7.** Crummy, A. B.: Wisconsin Med. J. *65*:84 (Feb.) 1966.

Contraindications: Contraindicated for persons sensitive to oral iodine compounds or for patients with combined renal and hepatic disease or severe kidney impairment. Gastrointestinal disorders, which may interfere with absorption, or liver dysfunction, which may result in inadequate biliary secretion of medium, are likely to result in unsatisfactory visualization.

Precautions and Side Effects: Mild and transient nausea, vomiting, or diarrhea sometimes occur; but the incidence can be reduced by using the calcium granules and restricting the dosage to 3 Gm. Transient headache, dysuria, or abdominal pains may occur.

Hypersensitivity reactions may include urticaria, serum sickness-like reactions (fever, rash, arthralgia), other skin reactions, and rarely anaphylactoid shock. They are more likely to occur in the individual with a history of allergy, asthma, hay fever, or urticaria and in the individual who is known to be hypersensitive to iodine compounds. Antihistamines and corticosteroids are used to control hypersensitivity reactions; but the occasional serious anaphylactoid reactions require the immediate use of epinephrine or phenylephrine, oxygen, and intravenous corticosteroids.

For full information see Package Insert.

Supply: The *calcium* salt (Oragrafin Calcium Granules) is available in single-dose foil packets providing 3 Gm. of calcium ipodate as Granules dispersed in flavored sucrose. The *sodium* salt is available in capsule form (Oragrafin Sodium Capsules) providing 0.5 Gm. sodium ipodate per capsule.

in oral cholangiography and cholecystography

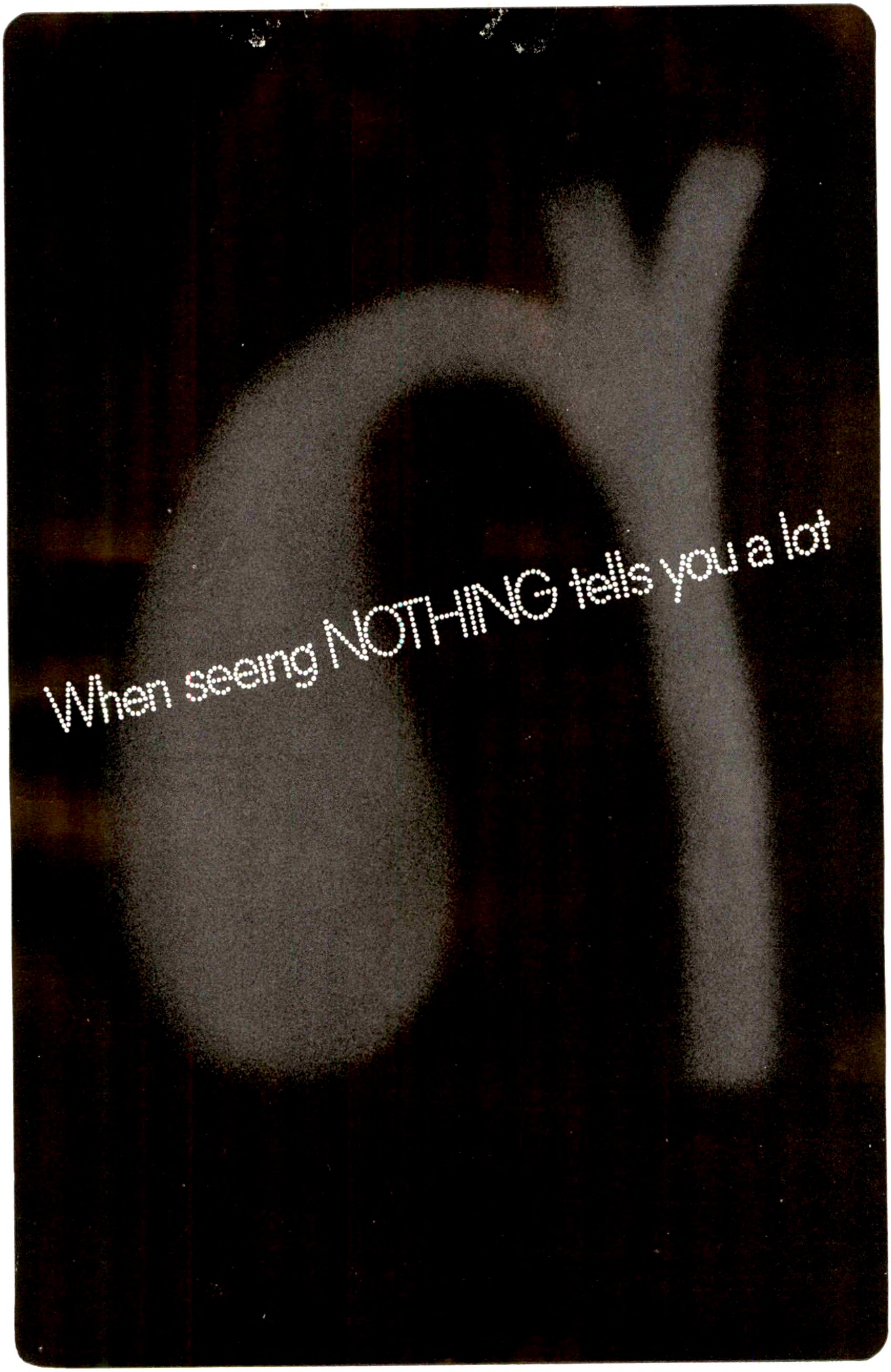
Oragrafin®

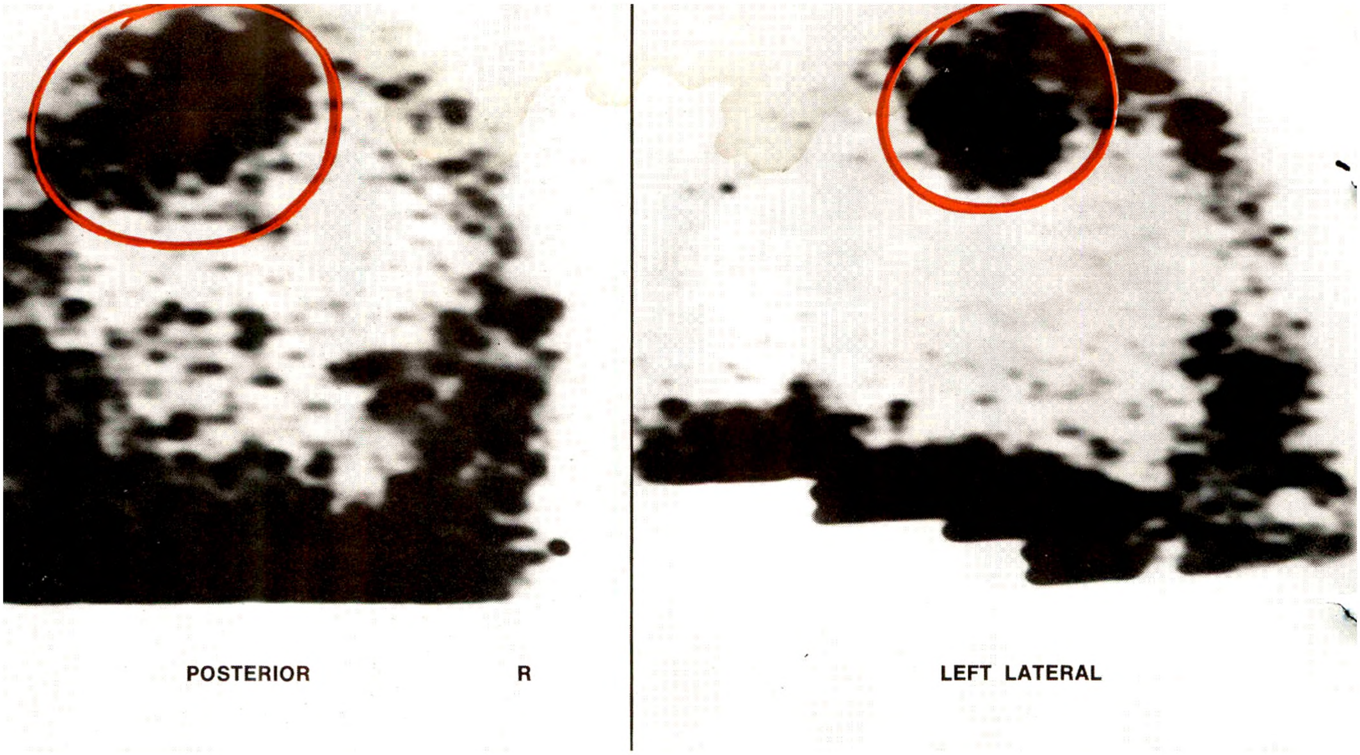
Squibb Ipodate

for maximum concentration with better patient toleration

SQUIBB

The Priceless Ingredient' in every product is the honor and integrity of its maker.


When seeing NOTHING tells you a lot



In suspected brain pathology, find out fast with **Pertscan**-99m

For brain scanning, Pertscan-99m provides more information with less radiation to the patient than any other related cerebral test—whether other radioisotopes or x-rays. And you get each projection fast—as little as 2 minutes with a camera, 15 minutes or less with rectilinear scanners.

A 54-year-old man was hospitalized with progressive weakness of the right side, followed by seizures of the right side (Jacksonian seizures). Brain scans showed an abnormal concentration of isotope in the left parasagittal area. Surgery revealed a meningioma, which was removed, and the patient recovered.

The 2 scans above, showing the marked abnormal uptake (which turned out to be a meningioma), were made with Pertscan-99m. This product is shipped Monday through Friday—and Sunday. Thus, brain scans can be scheduled 6 days a week—Monday through Saturday.

INDICATIONS: Adjunctive diagnostic aid in detecting and localizing intracranial neoplastic (primary or metastatic) and non-neoplastic lesions.

CONTRAINDICATIONS: Radio-pharmaceutical agents should not be administered to pregnant women or to persons less than 18 years old unless the indications are very exceptional.

PRECAUTIONS: Care should be taken to ensure minimum radiation exposure to the patient as well as all personnel; to prevent extracranial contamination because this can lead to erroneous interpretation; and to differentiate areas of abnormal activity from areas of normal vascular activity.

804464

Pertscan™-99m

SODIUM PERTECHNETATE Tc 99m

Also available:

Pertgen™-99m

TECHNETIUM 99m GENERATOR KIT

ABBOTT LABORATORIES NORTH CHICAGO, ILLINOIS

Abbott Laboratories, S.A., 2, rue Thalberg, 1201 Geneva, Switzerland

TM—Trademark

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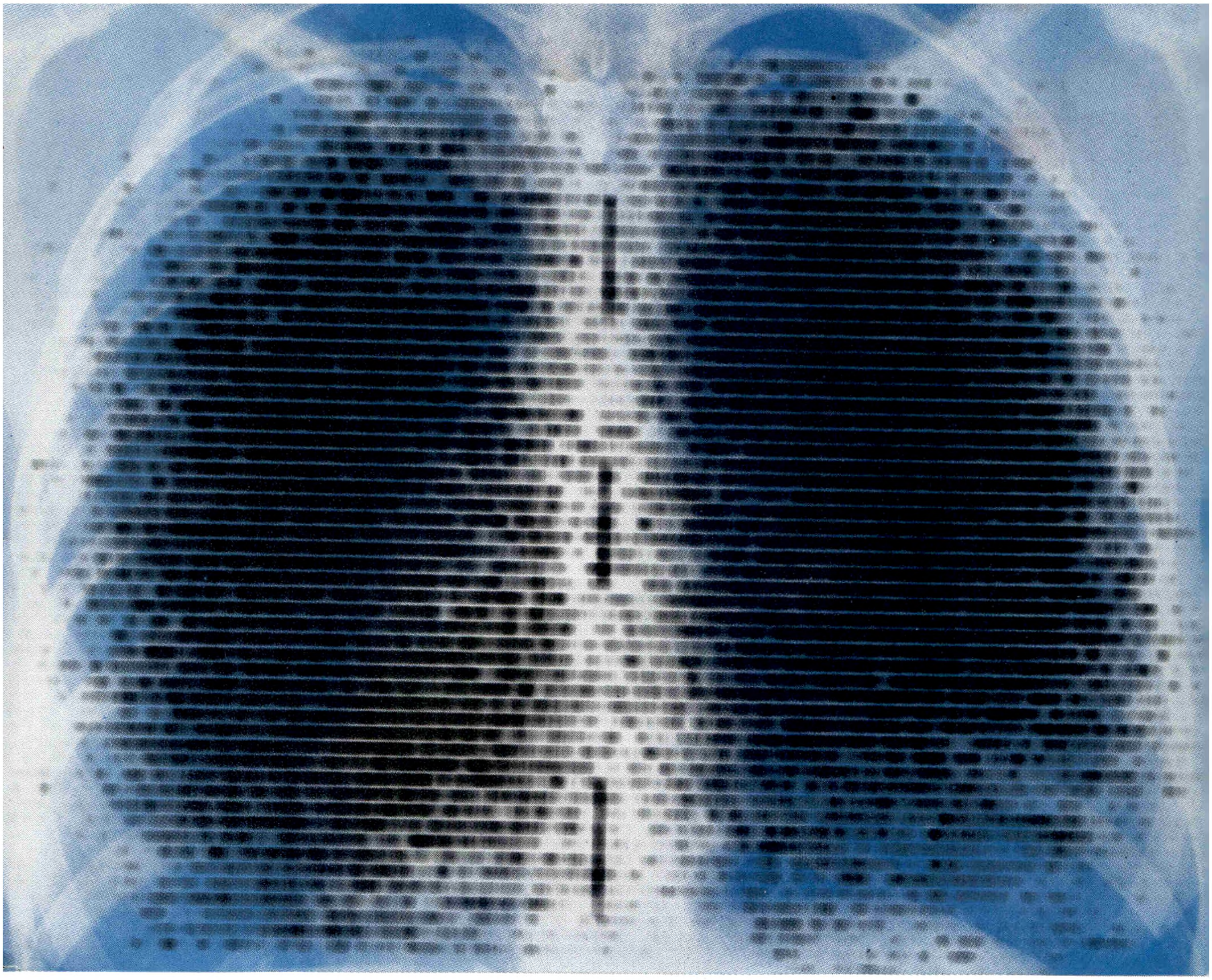


Abbott announces Macroscan™-131

AGGREGATED RADIO-IODINATED (I^{131}) ALBUMIN (HUMAN)

If it's a pulmonary problem, Macroscan-131 pictures it!

Pulmonary embolism, suspected: To confirm (or rule out) its occurrence.

Chronic pulmonary tuberculosis: To estimate unilateral and regional function and perfusion of the lungs.

Emphysema: To evaluate the degree of focal lack of perfusion.

Pneumonitis: To evaluate the decreased regional blood flow that occurs without obstruction of vessels.

Lung tumors: To evaluate the regional ischemia resulting from compression or obstruction of pulmonary arteries.

Surgery and/or other therapy for lung disorders: To evaluate the effectiveness of therapeutic measures.

Macroscan-131 is sterile and non-pyrogenic. It is ready to use and should not be heated prior to use.

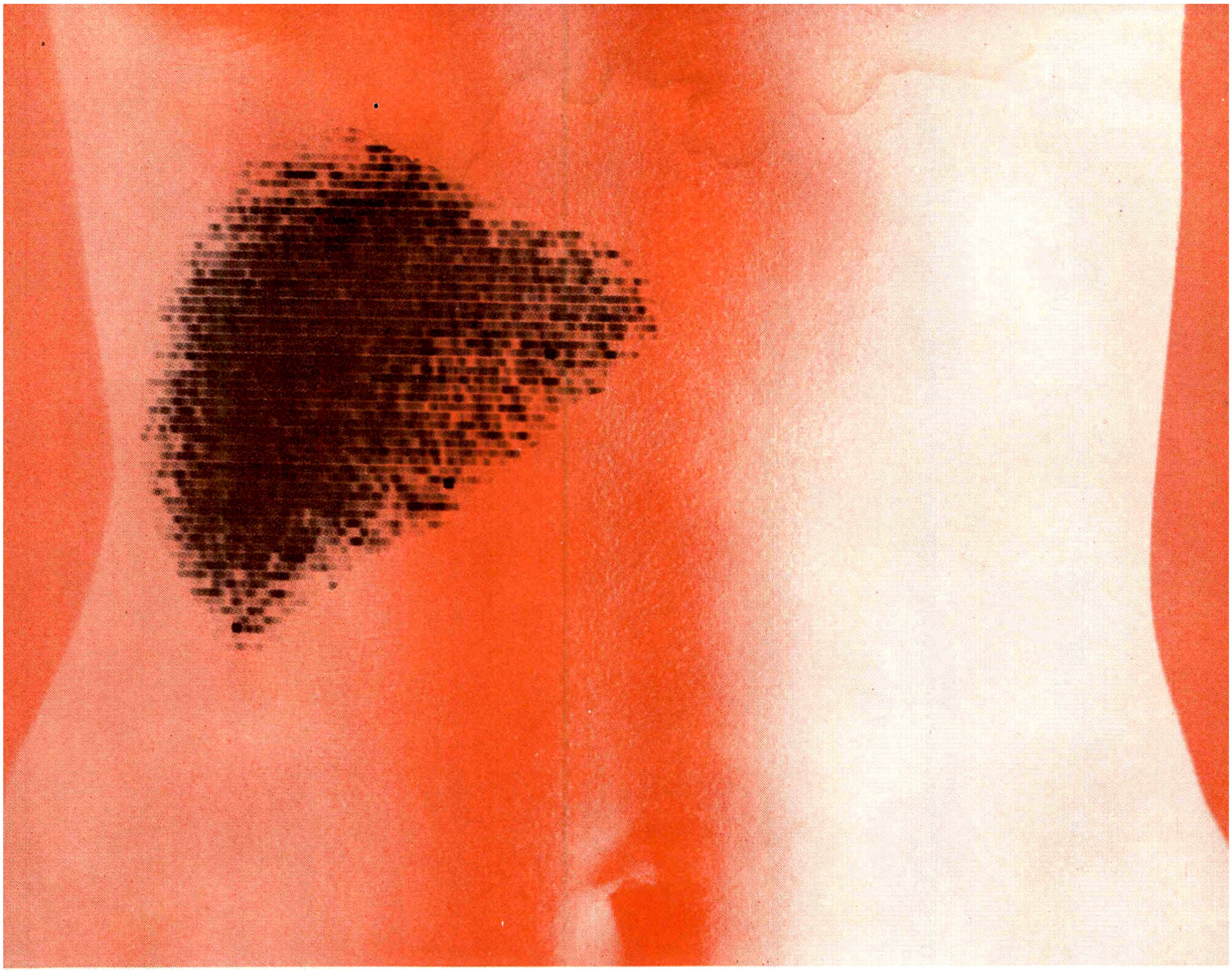
INDICATIONS: For scintillation scanning of the lungs to evaluate total, unilateral, and regional arterial perfusion to the lungs.

CONTRAINDICATION: Radio-pharmaceutical agents should not be administered to pregnant women, nursing mothers, or to persons less than 18 years old unless the indications are very exceptional.

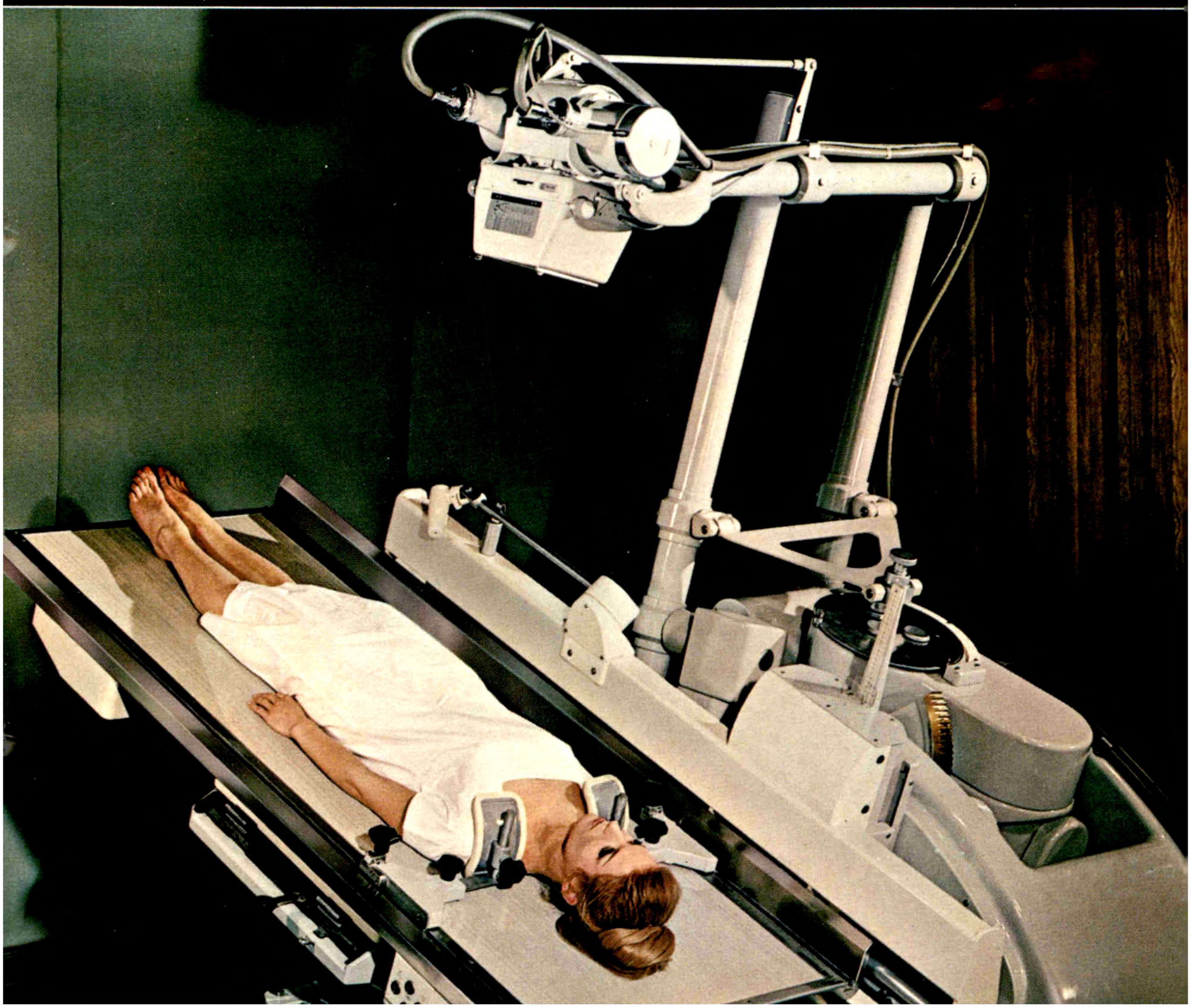
PRECAUTIONS, SIDE EFFECTS: Care should be taken to administer the minimum dose consistent with safety and validity of data. The possibility of an immunological response to albumin should be kept in mind when serial scans are performed. There is a theoretical hazard in acute cor pulmonale, because of the temporary small additional mechanical impediment to pulmonary blood flow. A possible case of urticara has been related to a similar preparation. The thyroid gland should be protected by prophylactic administration of concentrated iodide solution.

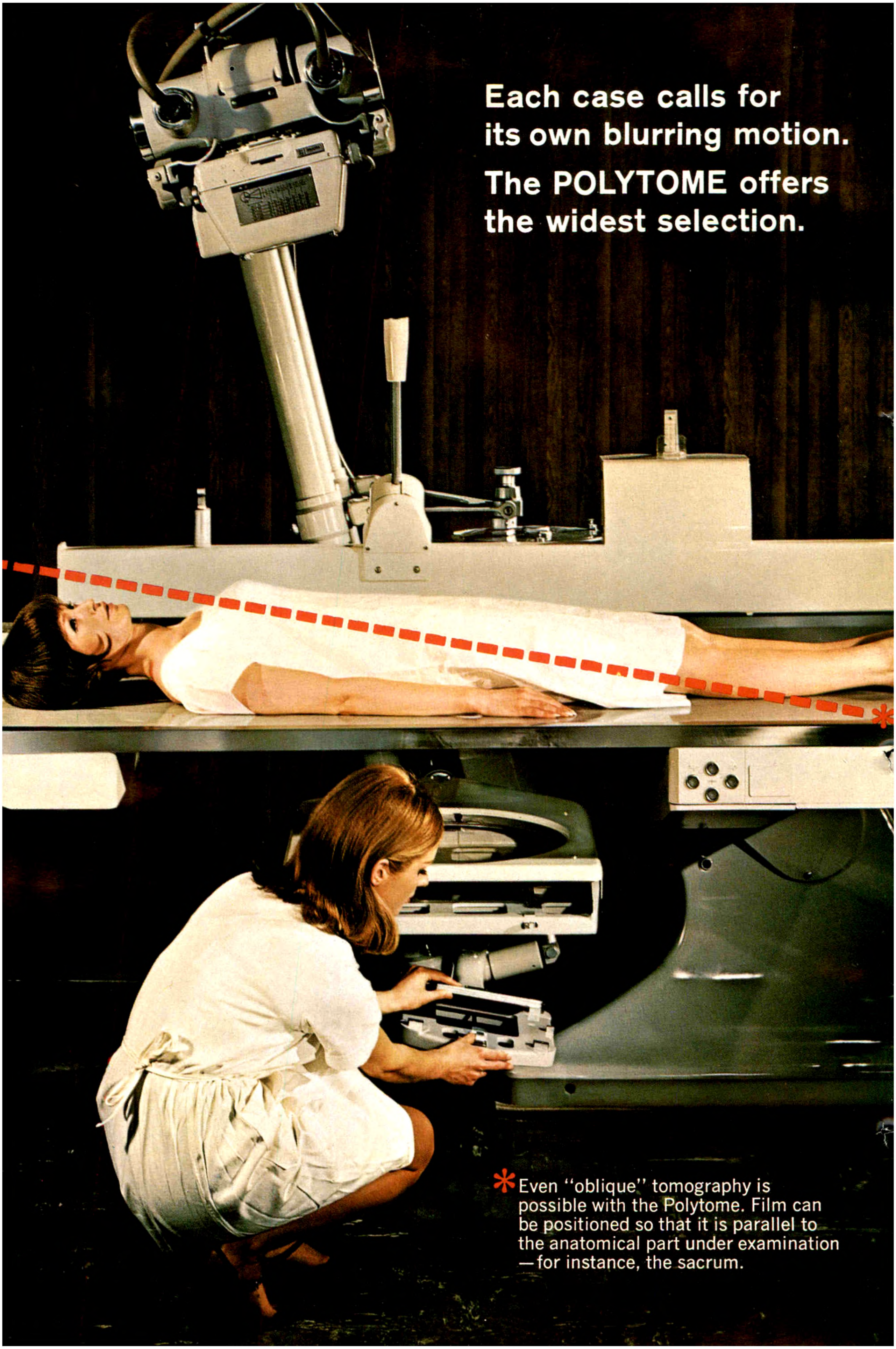
TM—TRADEMARK

804400



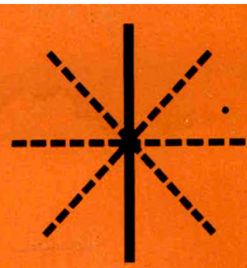
1. Gottschalk, A., J.A.M.A., 200:630, 1967.
2. Shingleton, W. W., et al., Ann. Surg., 163:685, 1966.




Each case calls for its own blurring motion.
The POLYTOME offers the widest selection.
*Even "oblique" tomography is possible with the Polytome. Film can be positioned so that it is parallel to the anatomical part under examination —for instance, the sacrum.

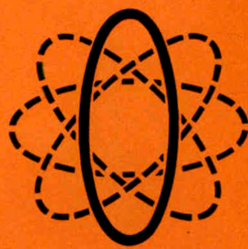
LINEAR

Linear motion provides excellent tomograms where short exposure times are necessary and where no bony structures lie parallel to the movement. The layer thickness may be varied, since the angle of swing can be adjusted between 10 and 50 degrees. Linear tube trajectory can be oriented throughout 360° for the Universal Polytome. Exposure times: 0.15-0.9 seconds.



ELLIPTICAL

With elliptical movement, blurring is complete at a maximum long axis angle of 40°. An apt compromise between linear and circular movement, elliptical combines many advantages of both. Elliptical movement can be oriented with reference to bony structures in the vicinity of the layer permitting full exploitation of optimum conditions without shifting the patient. Trajectory can also be positioned throughout 360° for Universal Polytome. Exposure time: 3 seconds.

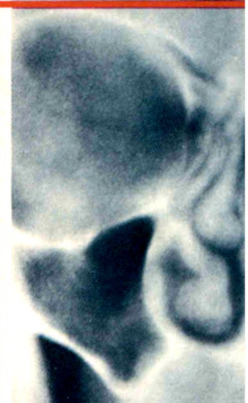


CIRCULAR

The simplest of the multi-directional movements, offers complete blurring with unchanging radius and angles of 29° and 36°. The choice of two angles provides a choice of two layer thicknesses. With the circular motion, however, rounded anatomical elements can create artefacts which can be eliminated with hypocycloidal motion. Exposure time: 3 seconds.

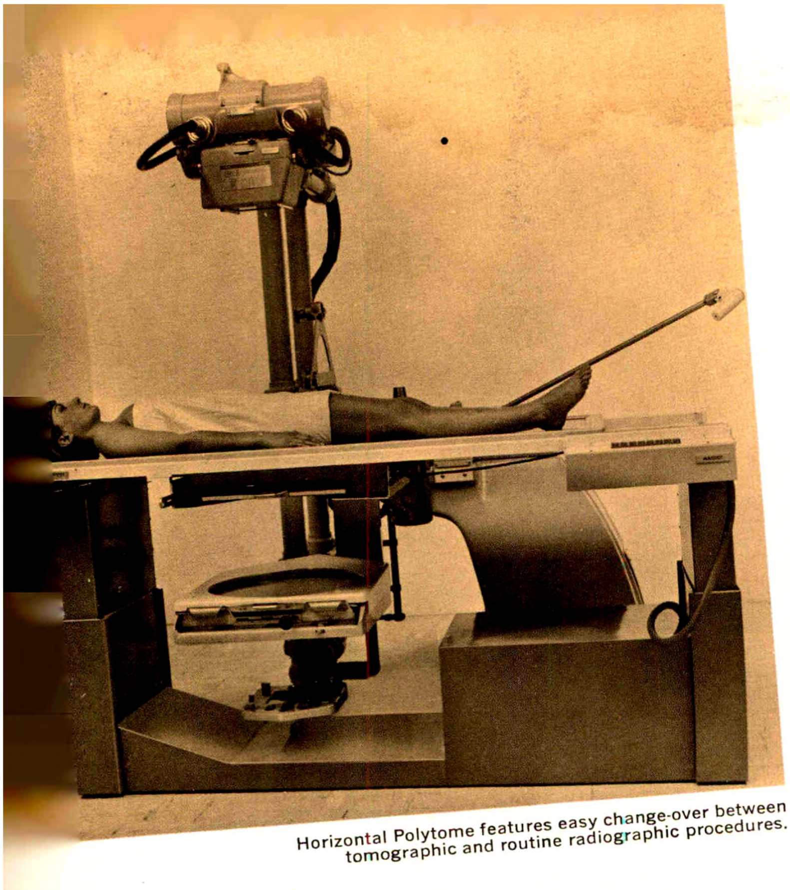
HYPOCYCLOIDAL—Unique with the Polytome

Hypocycloidal is the most sophisticated of the multi-directional movements—its angle of swing is 48°. It provides perfect blurring due to complex multi-direction and length of swing. All structures, bony or otherwise, lying outside the selected layer can be totally obscured. Since the x-rays traverse the object at continuously changing angles, there is no preferential direction of blur, resulting in true representation of the part under scrutiny. This movement opens up new regions inaccessible with any other technique. Exposure time: 6 seconds.



CIRCULAR ZONOGRAPHY

Is the art of depicting thicker sections or "zones" (from 6.7cm to 1mm) by choosing small to very small blurring angles. On the Polytome, circular zonography can be carried out with very narrow angles of swing *continuously* adjustable between 0° and 20°. In circular zonography the tube travels 3 times more than it would for the same given angle in linear zonography, therefore a cleaner, clearer cut is obtained. Since zonography produces exposures in which only elements considerably remote from the zone are blurred, zonograms have much of the sharpness of normal radiographs.



Horizontal Polytome features easy change-over between tomographic and routine radiographic procedures.

VERSATILE APPLICATION

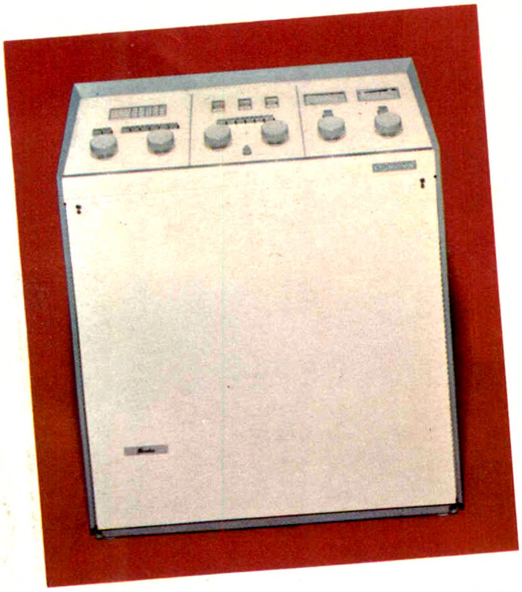
There are two models of the Polytome—Universa and Horizontal.

(A) The Universal version tilts from horizontal t vertical.

(B) The Horizontal Polytome provides the same wid range of blurring motions while limiting *table* pos tion to horizontal plane. An extra radiographic Buck is included.

Both versions of the Norelco Polytome System i clude these extra features:

- Heavy Polytome base, combined with Grossma principle of free-floating tube and film travel in arc circle — on one axis of rotation — avoids additio blur often arising from equipment instability.
- Constant exposure factors and collimation du exposure ensure constant film blackening and c stant magnification.
- Prefocused, easily removable grid always rot in perfect synchronization with tube and film for mum results.
- Two constant enlargement factors (1.3 and
- "Oblique" tomography with inclinable lower sette tray.
- Minimum Layer thickness of 1mm.
- Maximum Layer thickness of 6.7 cm.
- Unusual simplicity of operation, easy alterat blurring motions.



THE INTEGRATED SYSTEM

Research by leading users into factors which influence tomogram quality demonstrates that results are significantly improved with the use of our integrated system consisting of Norelco three-phase generators with Norelco Super Rotalix tubes.

M-38

Norelco® | **MEDICAL DIVISION**

NORTH AMERICAN PHILIPS COMPANY, INC.
100 East 42nd Street, New York, New York 10017

Serial angiography simplified: Picker calls in a computer.

Radiopaque injection. X-ray exposure. Patient shifting. Angiography obviously requires that these elements and others (e.g., ECG, cinefluorography, etc.) constantly mesh. Up to now, *people* had to do all the required monitoring, coordinating, synchronizing and operating to make angiography work, to make the elements mesh. No longer.

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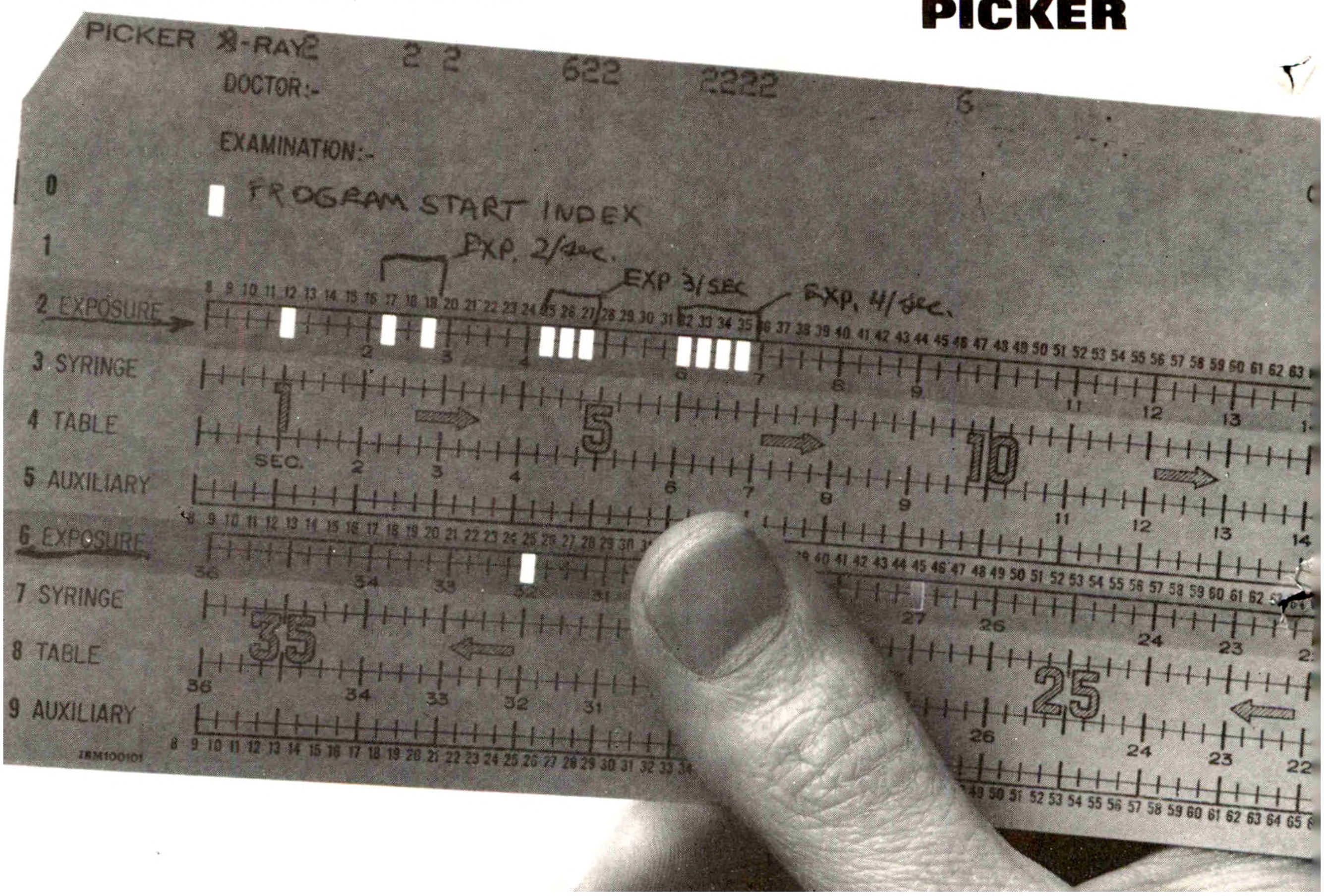

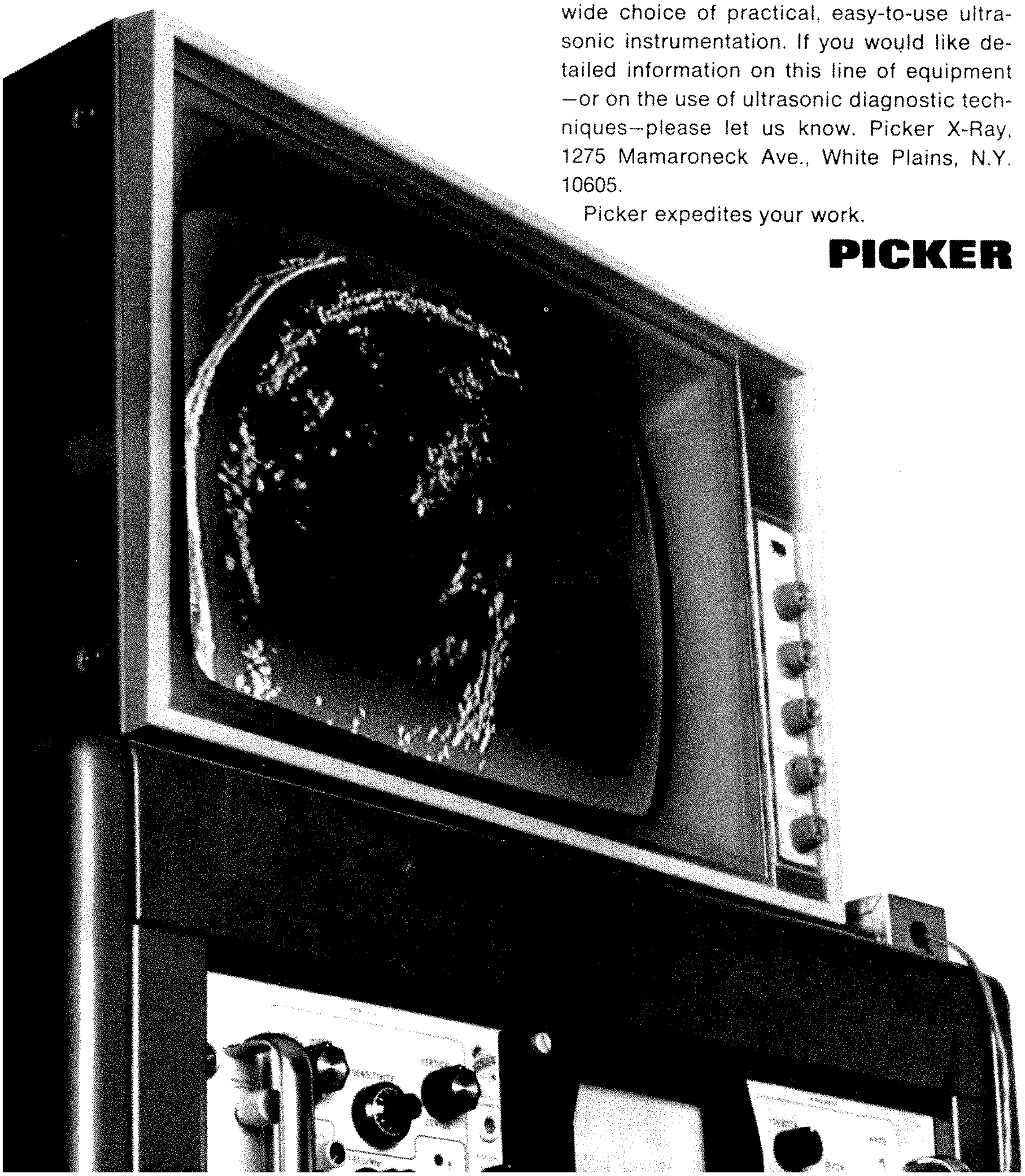

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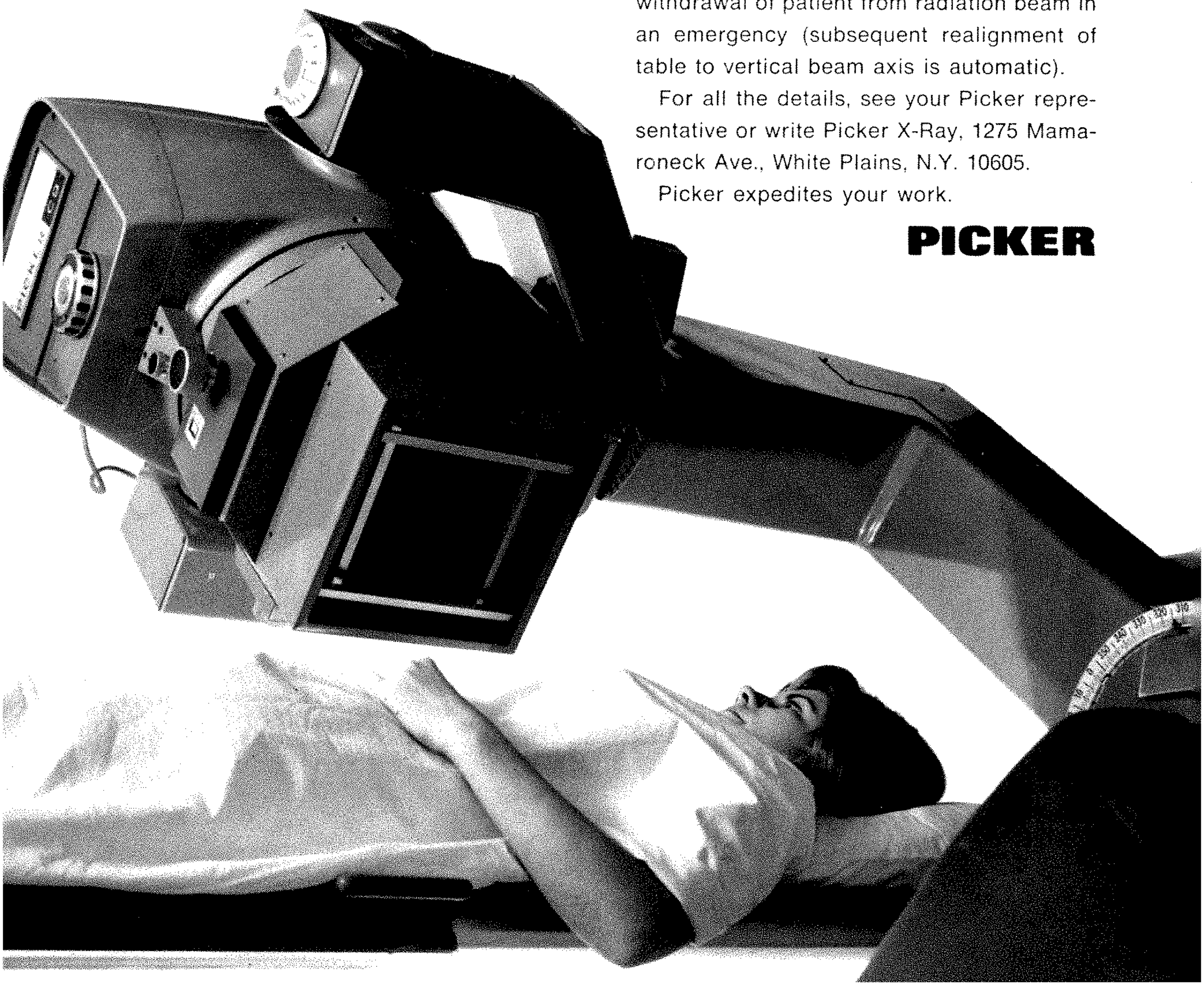

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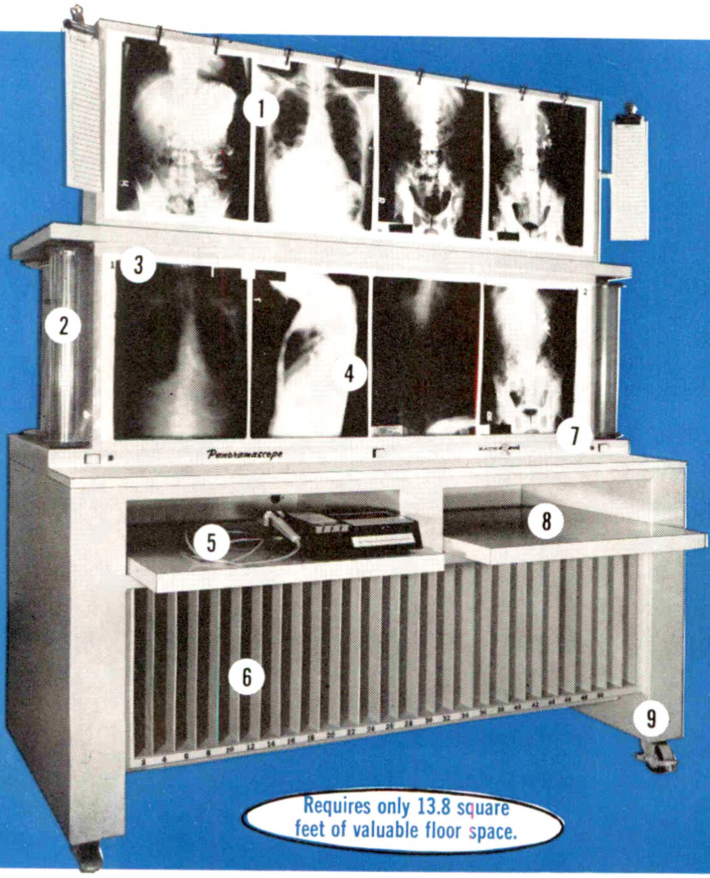

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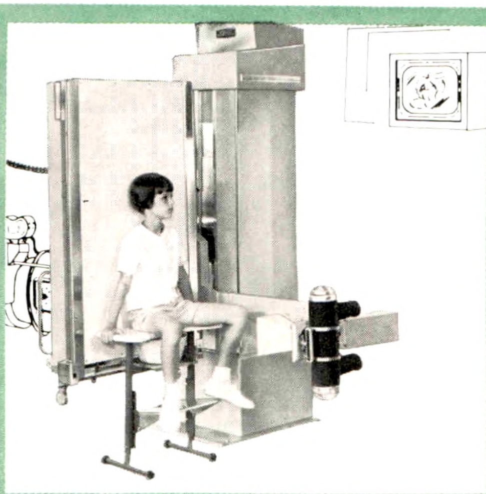

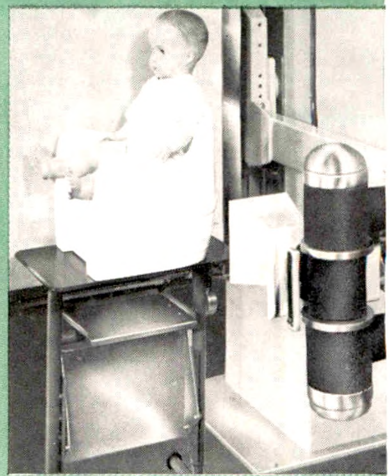

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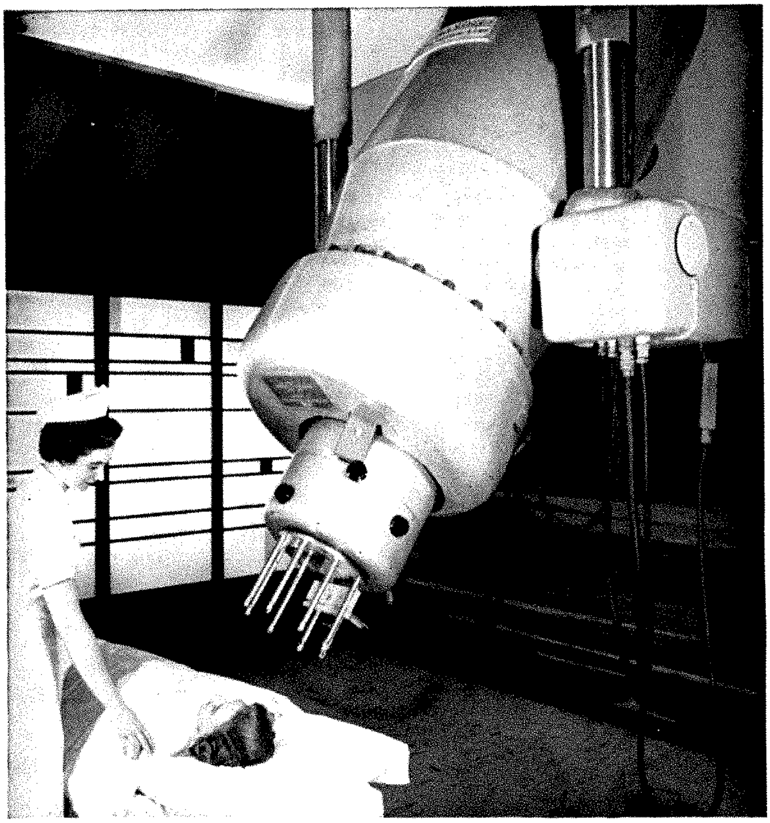

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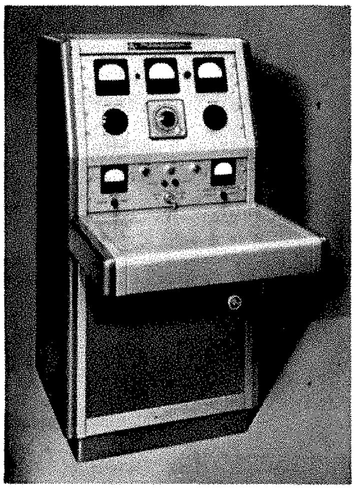

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THE INFANTILE SELLA TURCICA*

NEW ROENTGENOLOGIC AND ANATOMIC CONCEPTS BASED ON A DEVELOPMENTAL STUDY OF THE SPHENOID BONE

By E. LEON KIER, M.D.†

NEW YORK, NEW YORK

THE roentgenologic assessment of the sella turcica in infancy has remained difficult and controversial in spite of the extensive literature dealing with the J or omega-shaped sella. As a result of a previous study which investigated the roentgenologic implications of the developmental anatomy of the normal optic canal and its anomalies,[24] it became apparent that certain current roentgenologic interpretations of the sella in infancy are anatomically inaccurate. The continuing controversy regarding the clinical significance of certain roentgenologic features of the sella in infancy has resulted from the lack of objective criteria by which early pathologic changes can be differentiated from normal growth patterns. This communication will first describe an anatomic roentgenologic investigation providing these criteria. This will be followed by a reappraisal of the past literature in regards to the validity of previously presented descriptions, definitions and etiologies of sellar abnormalities in infancy.

The normal adult anatomy of the superior surface of the body of the sphenoid bone is shown in Figure 1, *A* and *B*. This study deals with the presellar sphenoid which consists of the planum (jugum) sphenoidale, limbus sphenoidalis, roof of the optic canal, chiasmatic sulcus (optic groove) and the tuberculum sellae (olivary eminence).[8,35,37] The term, tuberculum sellae, as used in this study refers to the anterosuperior margin of the sella turcica. The term, infantile sphenoid[21] will be used to describe cases in which the sphenoid sinus is roentgenologically not in contact with the superior surface of the presellar sphenoid (Fig. 2, *A* and *B*). The term, adult sphenoid, will denote cases in which the entire presellar sphenoid is pneumatized. These terms will be used irrespective of the

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† Winner of Memorial Medal Award of the Association of University Radiologists, 1967.

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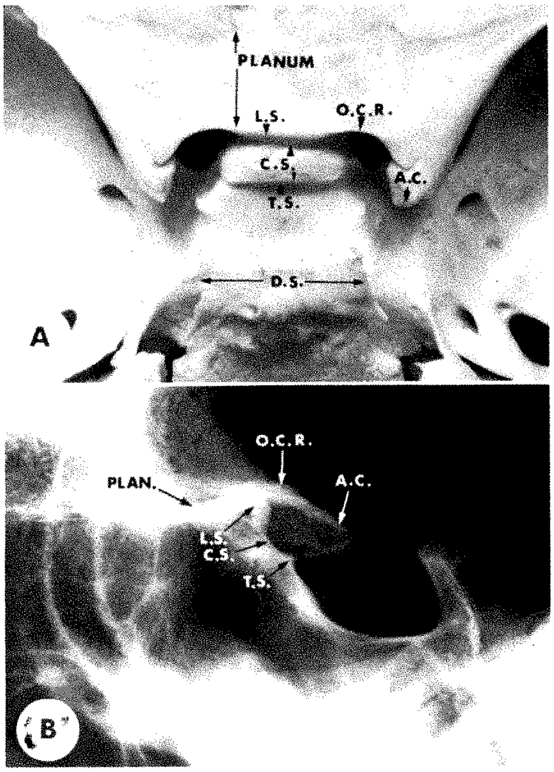


Fig. 1. Normal adult sphenoid. (*A*) Superior aspect of sphenoid bone specimen. (*B*) Lateral skull roentgenogram. Note that the optic canal roof (O.C.R.) is not a prominent structure in the lateral skull roentgenogram. A.C.=anterior clinoid process; C.S.=chiasmatic sulcus; D.S.=dorsum sellae; L.S.=limbus sphenoidalis; PLAN.=planum sphenoidale; T.S.=tuberculum sellae.

patient's age. The inferior root of the lesser sphenoidal wing will be referred to as the optic strut.[21]

MATERIAL AND METHODS

The anatomic material which formed the basis of this study (Table I) consisted of:

1. Twenty-six sphenoids examined in cleared and alizarin stained fetuses‡ ranging in age from 7 to 17 weeks of development.
2. Forty-five dissected sphenoid bodies in fetuses§ ranging from 20 to 40 weeks of development.
3. Eighteen dissected sphenoid bodies in infants§ younger than 5 years.
4. One hundred sphenoids examined in dry adult skulls,‖ age undetermined.

The roentgenologic material (Table II) consisted of lateral skull roentgenograms in:

1. Fifty fetuses ranging from 26 to 40 weeks of development.
2. Two hundred normal newborn infants.
3. One hundred normal children with infantile sphenoids.

‡ Obtained on loan from the Department of Anatomy, College of Physicians and Surgeons, Columbia University.

§ Obtained from the Department of Pathology, Yale University School of Medicine.

‖ Obtained in part from the Department of Anatomy Yale University School of Medicine.

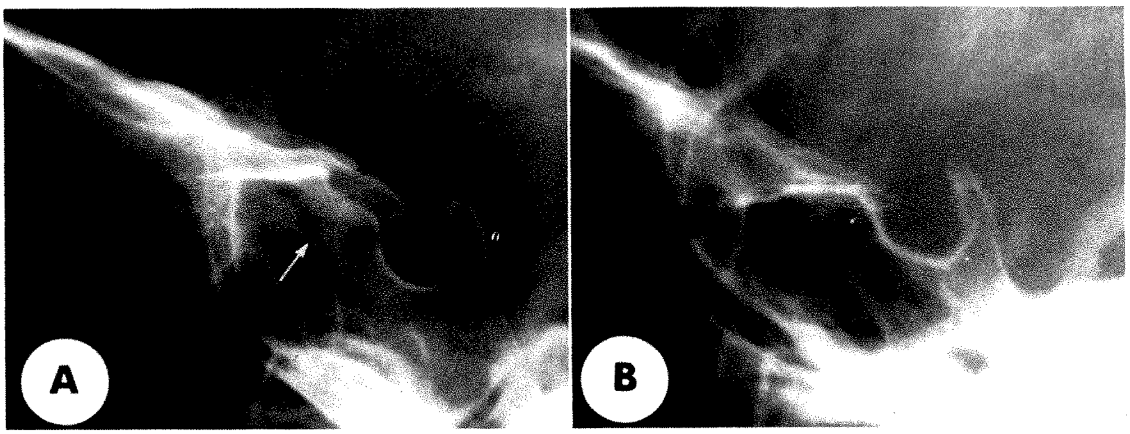


Fig. 2. Roentgenograms of children with normal infantile and adult type sphenoids. (*A*) In the infantile sphenoid, the upper wall of the sinus (arrow) is not in contact with the superior surface of the presellar sphenoid. (*B*) In the adult type sphenoid, pneumatization of the entire presellar region has resulted in the obliteration of distinct presellar structures.

TABLE I

ANATOMIC MATERIAL

Type of Anatomic Material	Age	Results of Study
26 cleared and alizarin stained fetuses 45 dissected fetal sphenoid bodies	7–17 weeks 20–40 weeks	Tuberculum sellae is the last region to ossify during prenatal period
18 dissected infant sphenoid bodies	<5 years	Variable posterior growth of planum sphenoidale determines width of chiasmatic sulcus
100 dry skulls	Adults	Appearance of chiasmatic sulcus and tuberculum sellae related to degree of sphenoid sinus pneumatization

TABLE II

ROENTGENOLOGIC MATERIAL

(Lateral skull roentgenograms)

Number	Age	Sphenoid Type	Clinical Status	Results of Study
50	Fetuses (26–40 weeks)			Progressive ossification of anterior sellar wall
200	Newborn		Normal	1. Planum sphenoidale not present 2. Distinct bony tuberculum sellae present in 98 per cent 3. Intrapresphenoid cartilage present in 15 per cent 4. Optic canal roof most superior sphenoid structure
100	Children	Infantile	Normal	1. Optic strut not fully visualized 2. Distinct tuberculum sellae present in all cases 3. Limbus sphenoidalis distinct from underlying sphenoid in 18 per cent
100	Children and Adults	Adult	Normal	Pneumatization of sphenoid sinus may obliterate chiasmatic sulcus and tuberculum sellae as distinct structures
50	Children and Adults	Adult	Abnormal	1. Pneumatized sphenoid may mask, distort and retard abnormal presellar changes 2. Rare presellar changes in craniopharyngioma
85	Children	Infantile	Abnormal	1. Craniopharyngioma—frequent presellar abnormalities 2. Posterior fossa tumors with normal head size—presellar abnormalities rare 3. Mental retardation with normal head size—no presellar abnormalities 4. Hydrocephalus with increased head size—direct relationship between head size and tuberculum sellae flattening 5. Optic glioma—misinterpreted roentgenograms most common in this condition 6. Gargoylism—presellar abnormalities present only with increased head size

4. One hundred normal cases with adult sphenoids.
5. Fifty cases with sellar abnormalities demonstrating an adult sphenoid.
6. Eighty-five children with abnormalities including intracranial neoplasms, hydrocephalus, mental retardation and miscellaneous skeletal problems. All these cases had infantile sphenoids.

Fetal age was determined by the crown-heel length[34] for the dissected specimens and by the occipitofrontal diameter[36] for the roentgenologic material. The fetal and infant specimens for dissection were obtained by *en bloc* excision of the body and lesser wings of the sphenoid bone during autopsy. Following fixation in 10 per cent formalin, the specimens were dissected free of their soft tissue and dural lining. The prenatal ossification and postnatal growth patterns were determined. The cleared and alizarin stained fetuses were examined and photographed, with transillumination as a light source.

Selected specimens were roentgenographed to determine the anatomic structures visualized in lateral skull projections. The effects of roentgen-ray tube angulation and skull rotation were investigated.

RESULTS

A. DEVELOPMENT OF THE SUPERIOR SURFACE OF THE BODY OF THE SPHENOID ANTERIOR TO THE FLOOR OF THE SELLA TURCICA

This development can be divided into 4 stages: (1) chondrification of the sphenoid body; (2) prenatal ossification; (3) postnatal development of the planum sphenoidale; and (4) variable posterior growth of the planum sphenoidale.

Stage 1. Chondrification of the sphenoid body. This stage was not investigated in the present study. According to Augier,[1] chondrification first occurs behind the pituitary gland. The cartilaginous plate extends forward surrounding the stalk of Rathke's pouch and forms the cartilaginous presphenoid anteriorly. Fawcett[14] states that the dorsum sellae chondrifies independently of the rest of the sphenoid.

Stage 2. Prenatal ossification. The last region of the superior surface of the sphenoid body to ossify, except for the dorsum sellae, is the anterosuperior margin of the sella. At the 16 week stage of fetal development (Fig. 3*A*) the floor of the sella formed by the ossified postsphenoid is present. The lesser sphenoidal wings are well ossified. The lateral presphenoid center outlining the medial border of the optic foramen and a small deep middle presphenoid center are present. The region of the anterior wall of the sella is still cartilaginous, round and superiorly convex. The term olivary eminence[26] is an appropriate description. This cartilaginous presphenoid olivary eminence is delimited posteriorly by the sharp anterior margin of the postsphenoid; laterally by the bony union of the pre- and postsphenoid at the level of the optic strut; and anteriorly by the paired lateral and single middle presphenoid centers.[25,42]

The cartilaginous presphenoid eminence becomes gradually ossified, in the last trimester, by backward and medial growth of the presphenoid centers[28] (Fig. 3, *A–D*; and 4, *A–D*). A progressively smaller column of cartilage is found at the center of the ossifying presphenoid in the region of the anterior sellar wall—the future tuberculum sellae. This central cartilaginous column extends from the superior to the inferior surfaces of the sphenoid body. At birth the superior end of this column is ossified, although at times quite fragile. The intrasphenoidal portion of this column may not be completely ossified until the end of the first year of postnatal life.

Thus at birth (Fig. 3*D*) the superior surface of the sphenoid body consists of: (1) the ossifying dorsum sellae; (2) the ossified postsphenoid (sellar floor); and (3) the ossified presphenoid forming the anterosuperior wall of the sella and extending anteriorly towards the cribriform plate. Of note is the superior position of the roof of the optic canals on either side of the presphenoid.

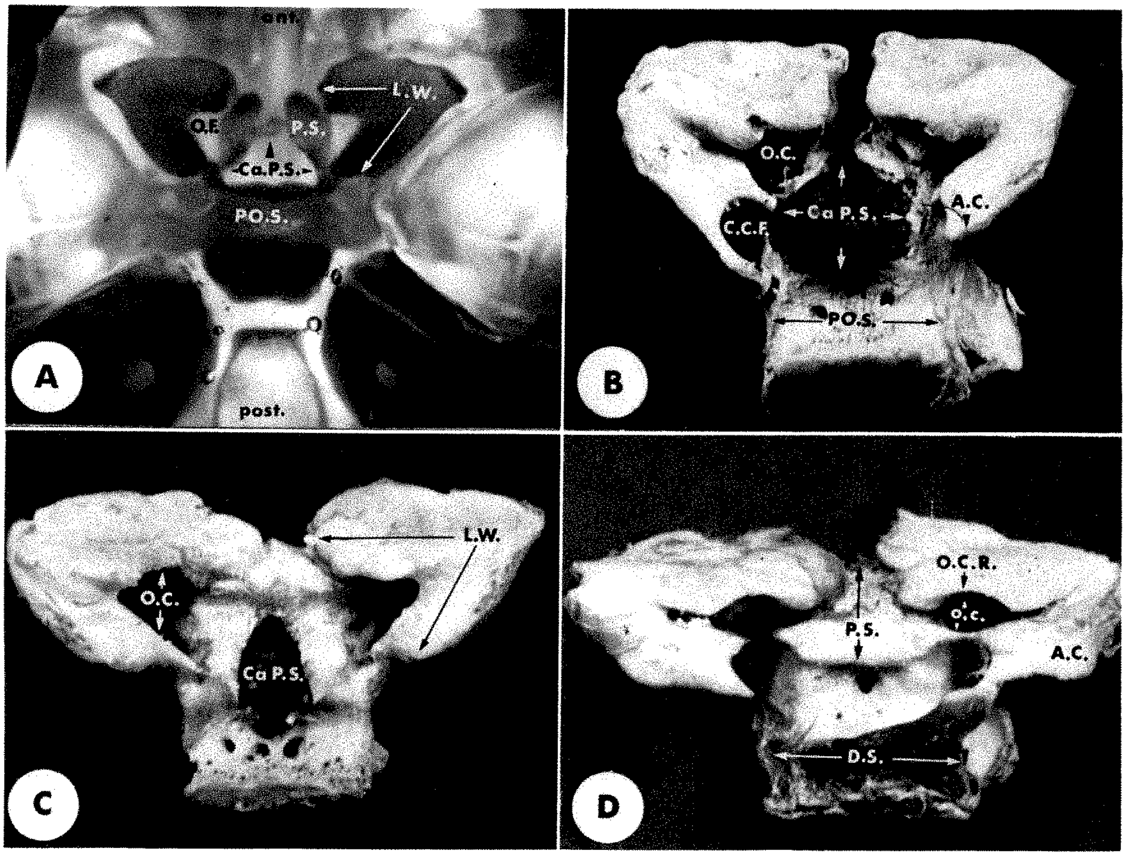


FIG. 3. Superior aspect of fetal sphenoidal bone specimens showing ossification of the presphenoid. (*A*) Cleared and alizarin stained skull base of a 16 week fetus (cartilage appears white, ossification centers appear black). The central presphenoid is still cartilaginous (Ca. P. S.). L. W. = lesser sphenoidal wing; O. F. = optic foramen; P. S. = ossified presphenoid; PO. S. = postsphenoid (floor of sella). (*B*) Dissected sphenoid specimen of a 20 week fetus. Note the large round (olivary) cartilaginous eminence of the presphenoid (Ca. P. S.) anterior to the floor of the sella. A. C. = anterior clinoid process; C. C. F. = caroticoclinoid foramen; O. C. = optic canal. (*C*) Dissected sphenoid specimen of a 32 week fetus. Note the diminishing size of the cartilaginous presphenoid (Ca. P. S.). (*D*) Dissected sphenoid specimen of a 4 day old infant. The superior surface of the presphenoid is completely ossified. Note the superior position of the optic canal roof (O. C. R.) as compared with the presphenoid (P. S.). D. S. = dorsum sellae.

Stage 3. Postnatal development of the planum sphenoidale. At birth, the planum sphenoidale, the smooth superior surface of the anterior sphenoid joining the two lesser sphenoidal wings, is not as yet formed (Fig. 3*D*). During the first year of life the medial center of the presphenoid continues to enlarge in height, eventually fusing with the anterosuperior roots of the lesser sphenoidal wings (Fig. 5*A*). This fusion results in the formation of the planum sphenoidale. The two anterosuperior roots of the lesser sphenoidal wings may enlarge and meet in the midline without the participation of the middle presphenoid center.[18,39]

Stage 4. The variable posterior growth of the planum sphenoidale. The planum sphenoidale may continue to enlarge in width by variable posterior growth. This growth occurs mainly in the first year of life and overlaps the superior surface of the presphenoid. During this growth the posterior margin of the planum—the limbus sphenoidalis—is separate from the underlying presphenoid (Fig. 5, *A*, *B* and *C*; and 6, *A*, *B* and *C*). This separation may remain

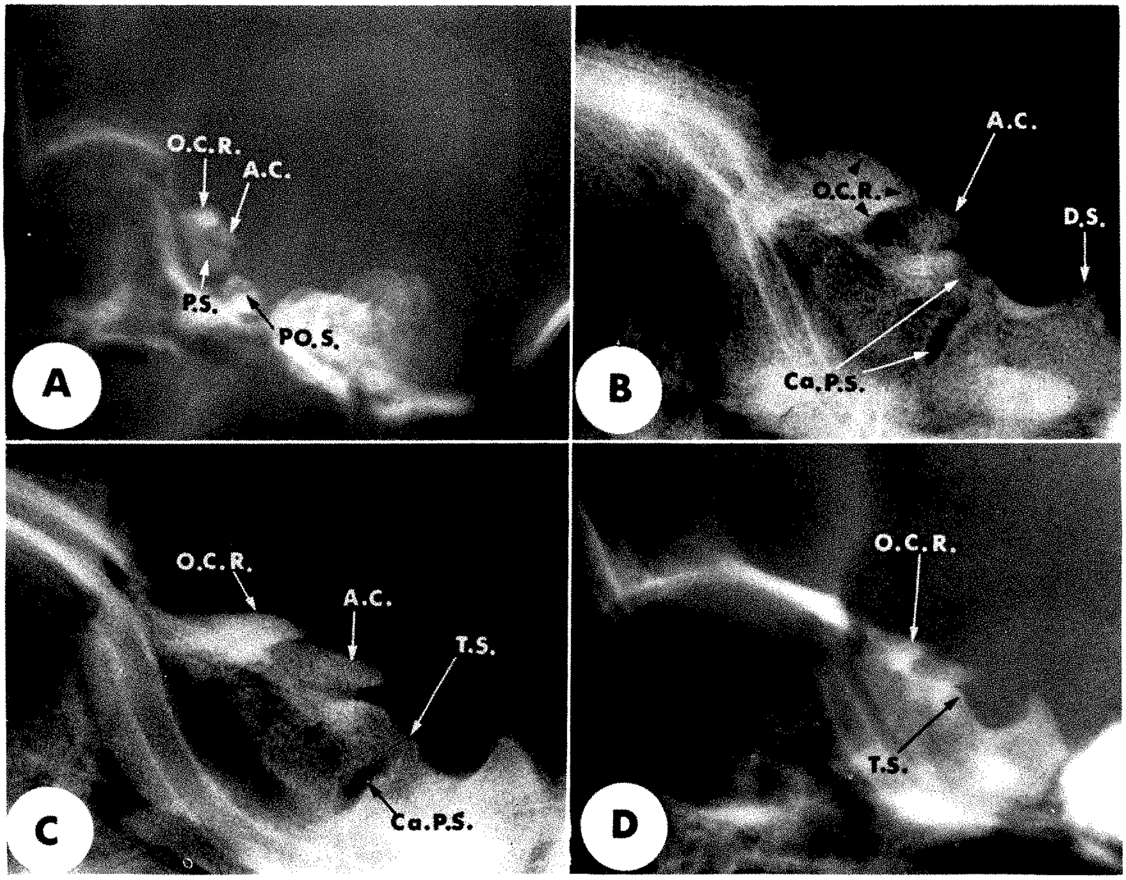


Fig. 4. Lateral skull roentgenograms showing ossification of the presphenoid. Developmental stages comparable to those in Figure 3. (*A*) A 28 week fetus. The region of the future tuberculum sellae is not as yet ossified. Note the superior position of the optic canal roof (O. C. R.). A. C. = anterior clinoid process; P. S. = presphenoid; PO. S. = postsphenoid (floor of sella). (*B*) A 34 week fetus. The anterior sellar wall is partially ossified. Note the size and prominence of the optic canal roof (O. C. R). The "intersphenoid synchondrosis" is actually the centrally located remnant of the cartilaginous presphenoid (Ca. P. S.). D. S. = dorsum sellae. (*C*) A 38 week fetus. The tuberculum sellae (T. S.) is further ossified. Note the flattening of the optic canal roof. (*D*) Normal 2 week old infant. Note the following features of the normal newborn sphenoid; (1) a planum sphenoidale is not present; (2) the anterosuperior margin of the sellar fossa—the tuberculum sellae (T. S.) is ossified and well defined; (3) the optic canal roof is prominent and the most superior sphenoid structure.

present for a long period following the development of the planum (Fig. 7, *A*, *B* and *C*). In the adult the 2 structures are fused together.

The configuration of the superior surface of the definitive presellar sphenoid is governed by these variations in the posterior growth of the planum.[35,37] The region of the presphenoid not overlapped by the planum, will remain as the definitive chiasmatic sulcus. Thus a narrow planum will be associated with a wide chiasmatic sulcus (Fig. 8, *A–D*). A wide planum will be associated with a narrow chiasmatic sulcus.

The posterior growth of the planum also increases the length of the optic canal roof which grows over the anterior clinoid process (Fig. 8*D*).

B. THE NORMAL ROENTGENOGRAPHIC NEWBORN SPHENOID

Lateral skull roentgenograms of 200 normal newborn infants were reviewed and the following features noted (Fig. 4*D*):

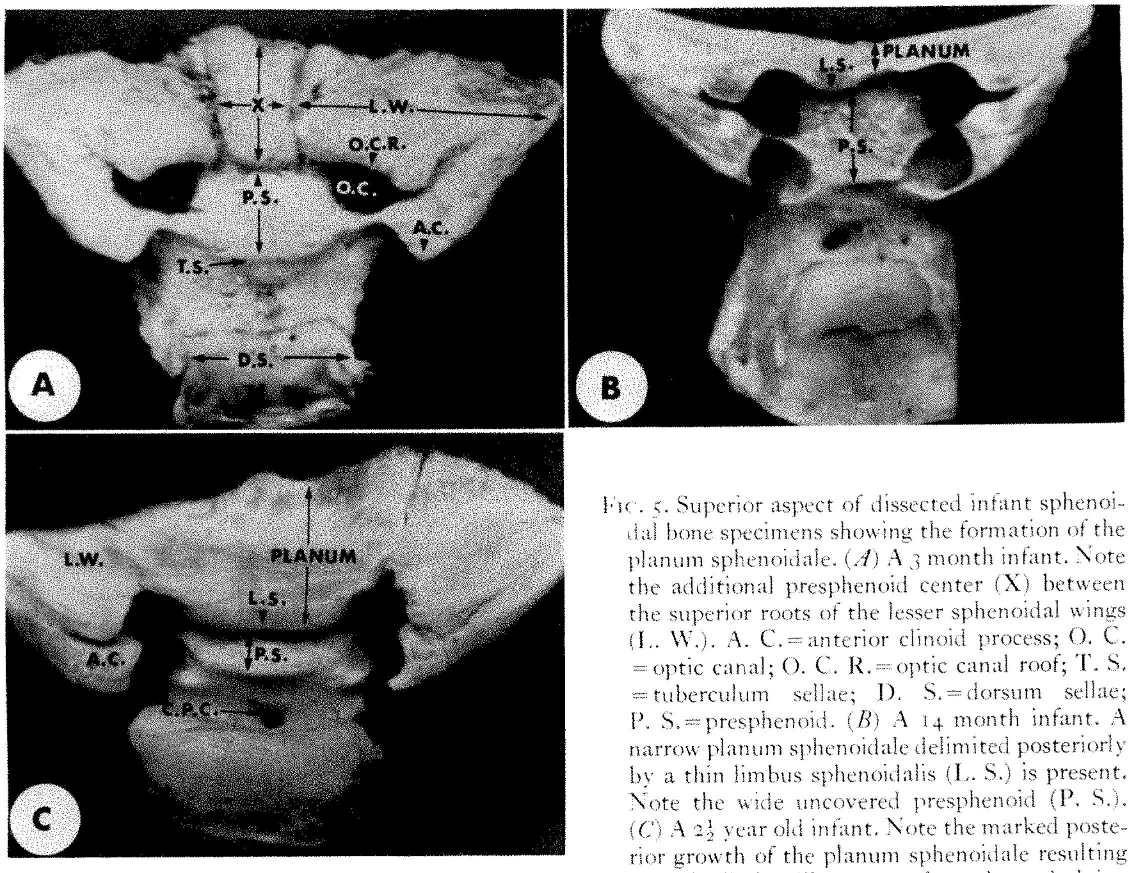


Fig. 5. Superior aspect of dissected infant sphenoidal bone specimens showing the formation of the planum sphenoidale. (*A*) A 3 month infant. Note the additional presphenoid center (X) between the superior roots of the lesser sphenoidal wings (L. W.). A. C.=anterior clinoid process; O. C. =optic canal; O. C. R.=optic canal roof; T. S. =tuberculum sellae; D. S.=dorsum sellae; P. S.=presphenoid. (*B*) A 14 month infant. A narrow planum sphenoidale delimited posteriorly by a thin limbus sphenoidalis (L. S.) is present. Note the wide uncovered presphenoid (P. S.). (*C*) A $2\frac{1}{2}$ year old infant. Note the marked posterior growth of the planum sphenoidale resulting in almost total coverage of the presphenoid. The limbus sphenoidalis is still separate from the underlying presphenoid (see Figure 6*C*). C. P. C.=craniopharyngeal canal.

(1) a planum sphenoidale was not present; (2) a distinct and ossified anterosuperior margin of the sella—the tuberculum sellae—was present in 98 per cent of the cases; (3) 15 per cent showed the presence of intrasphenoid cartilage column—the so-called intrasphenoid synchondrosis (Fig. 6*A*); (4) the roof of the optic canal presented as the most superior sphenoid structure; and (5) the craniopharyngeal canal was not visualized.[28]

C. THE NORMAL ROENTGENOGRAPHIC INFANTILE SPHENOID

Lateral skull roentgenograms of 100 normal children with an infantile sphenoid were reviewed and the following features noted: (1) all cases had a distinct anterosuperior margin of the sella—tuberculum sellae; (2) 18 per cent showed the limbus sphenoidalis to be unfused to the underlying sphenoid (Fig. 7, *A*, *B* and *C*); and (3) the optic strut was seen only faintly through the presellar sphenoid (Fig. 11, *A* and *B*).

D. THE ABNORMAL ROENTGENOGRAPHIC INFANTILE SPHENOID

The following were found to be the features of presellar abnormalities in the lateral roentgenogram of the infantile sphenoid: (1) an absent tuberculum sellae (Fig. 9, *A*, *B* and *C*); (2) clear visualization of the optic strut (Fig. 12, *A–D*); and (3) true excavation of the chiasmatic sulcus (Fig. 14, *A* and *B*). An analysis of the abnormal infantile material in this study will be presented in the discussion section.

E. THE ADULT PRESELLAR SPHENOID

The normal adult anatomic and roentgenographic material demonstrated that

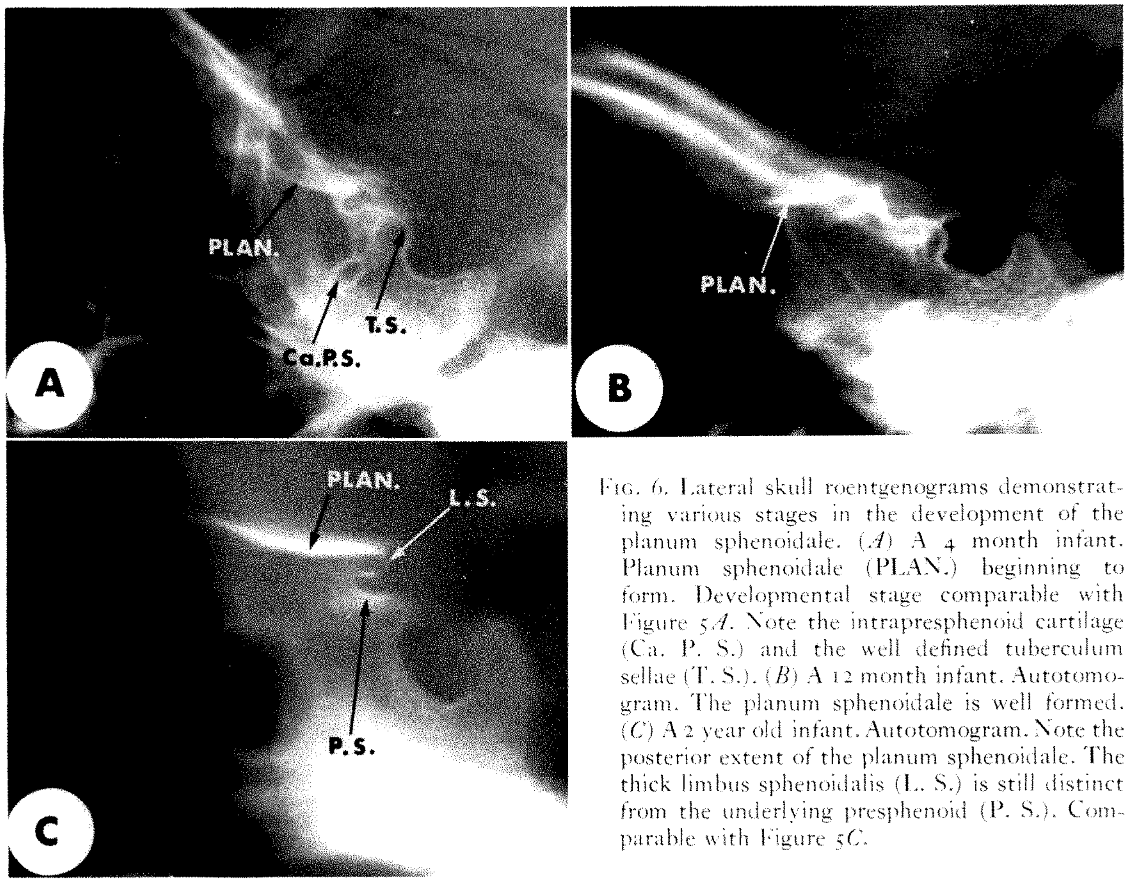


Fig. 6. Lateral skull roentgenograms demonstrating various stages in the development of the planum sphenoidale. (*A*) A 4 month infant. Planum sphenoidale (PLAN.) beginning to form. Developmental stage comparable with Figure 5*A*. Note the intrapresphenoid cartilage (Ca. P. S.) and the well defined tuberculum sellae (T. S.). (*B*) A 12 month infant. Autotomogram. The planum sphenoidale is well formed. (*C*) A 2 year old infant. Autotomogram. Note the posterior extent of the planum sphenoidale. The thick limbus sphenoidalis (L. S.) is still distinct from the underlying presphenoid (P. S.). Comparable with Figure 5*C*.

pneumatization of the sphenoid sinus results in many changes of the appearance of the presellar region.[23] There is frequent obliteration of the tuberculum sellae and chiasmatic sulcus as distinct structures (Fig. 2*B*). The most serious problem noted in this study was the masking of abnormal presellar features by a developing sinus. This is demonstrated by the case shown in Figure 13, *A* and *B*.

Analysis of the adult roentgenographic material with abnormalities revealed that pneumatization of the presellar sphenoid increases this region's resistance to erosion. This is demonstrated by the case shown in Figure 10, *A* and *B*. These observations appear to confirm Mahmoud's[29] findings that close association of the sphenoid sinus with the floor of the sella turcica plays an important role in retarding pathologic changes in the latter when intracranial tumors are present.

It appears then that the development of the sphenoid sinus may mask or retard the appearance of pathologic presellar changes. For these reasons the criteria of abnormality of the infantile sphenoid may not be found in cases in which the sphenoid sinus wall is in contact with the superior surface of the presellar sphenoid.

DISCUSSION

The continuing controversy regarding the clinical significance of certain roentgenologic features of the infantile sella could be due to 2 factors: (1) marked normal variability precludes the differentiation of the normal presellar sphenoid from pathologic changes; or (2) certain descriptions and definitions of the normal and abnormal infantile sella as presented in the literature are invalid.

The first factor has been investigated by this study in which we have correlated the

developmental anatomy of the normal presellar sphenoid with its roentgenologic manifestations. With this information pathologic changes in the infantile sphenoid can be differentiated from the normal growth patterns.

Burrows'[4] comprehensive review points out the extensive literature describing the presence of the so-called J or omega shaped sella in many different pathologic conditions as well as in normal cases. A review of this literature confirms Du Boulay's[9] conclusion that this whole subject still awaits clarification. A reappraisal of the previous literature was undertaken to assess the following points: (A) do the written descriptions correctly describe the accompanying roentgenograms?; (B) are the descriptive terms such as the J or omega-shaped sella meaningful and have they been used appropriately?; (C) do the many pathologic conditions described in the literature actually demonstrate presellar abnormalities?; and (D) which of the many factors invoked as the etiology for presellar abnormalities are significant?

A. THE DESCRIPTIVE ROENTGENOGRAPHIC CORRELATION

The following descriptive terms presented in the literature were evaluated as to their accuracy in describing the accompanying roentgenograms.

(*a*) "*Excavation under the anterior clinoid process.*" Many authors in the literature describe their cases as showing an abnormal "excavation under the anterior clinoid process" or an "excavated chiasmatic sulcus." These reports, however, present normal roentgenograms. Timme[43] and others,[17,30,38] utilized tracings of lateral skull roentgenograms to illustrate the

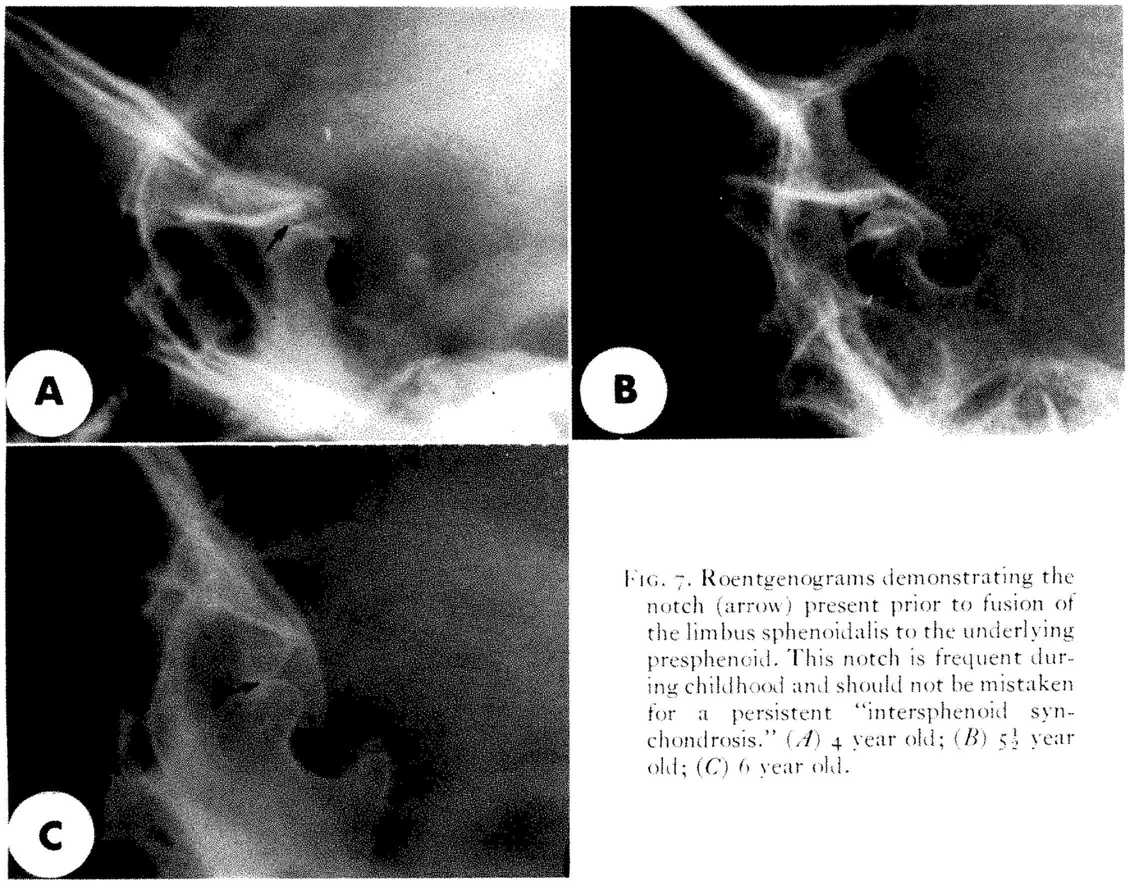


Fig. 7. Roentgenograms demonstrating the notch (arrow) present prior to fusion of the limbus sphenoidalis to the underlying presphenoid. This notch is frequent during childhood and should not be mistaken for a persistent "intersphenoid synchondrosis." (*A*) 4 year old; (*B*) $5\frac{1}{2}$ year old; (*C*) 6 year old.

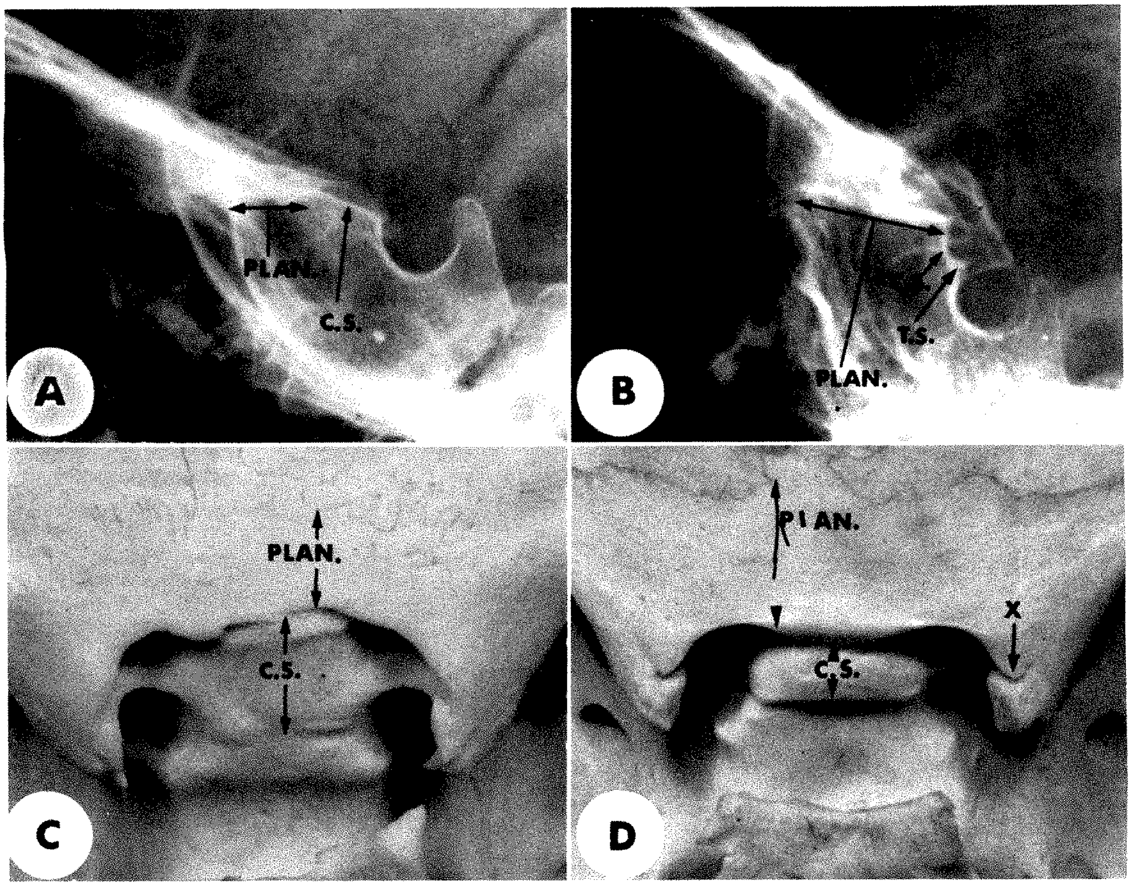


Fig. 8. The definitive presellar sphenoid. (*A* and *B*) Roentgenograms of children and (*C* and *D*) views of the superior surface of adult sphenoid specimens, demonstrating the inverse relationship between the widths of the planum sphenoidale (PLAN.) and chiasmatic sulcus (C.S.). Note the vertical chiasmatic sulcus and small tuberculum sellae (T. S.) in *B*. X = overgrowth of the anterior clinoid by the optic canal roof.

normal and "excavated" sphenoid. This study has elucidated the anatomic components of the so-called excavation (Fig. 15, *A–E*). In the newborn the roof of the optic canal is a prominent sphenoid structure. In infancy the optic canal roof retains its prominence because of its posterior growth over the anterior clinoid process during the development of the planum sphenoidale. Roentgenographically, the optic canal roof projects as a distinct curved line which forms the superior component of the "excavation." When the optic canal roof is disregarded, it can be noted that the normal chiasmatic sulcus is continuous with the planum sphenoidale without evidence of true excavation. An imperfect lateral roentgenogram (Fig. 16, *A* and *B*) markedly accentuates this "excavation." In the normal adult the optic canal roof is not a prominent structure because of its fusion to the anterior clinoid process (Fig. 1, *A* and *B*).

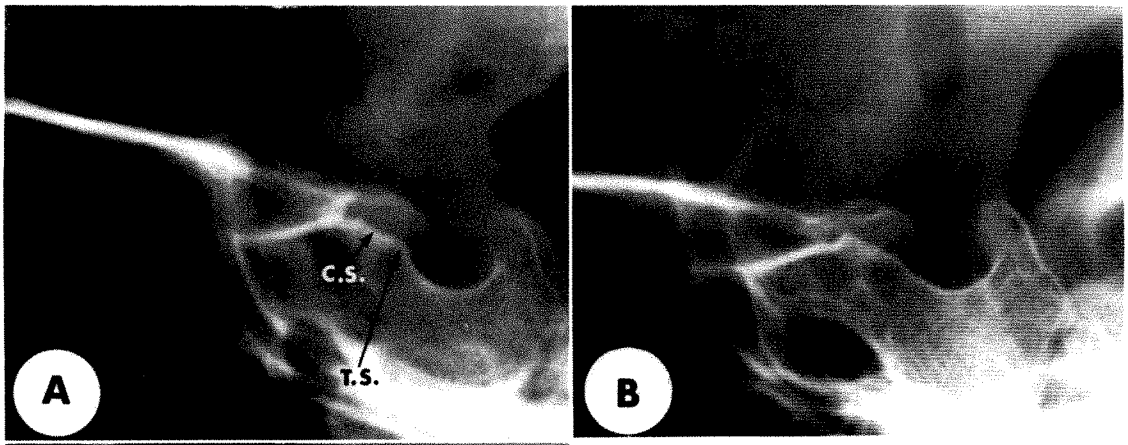
(*b*) "*Anterior extension of the pituitary fossa.*" Martin and Cushing[30] introduced this term in their classic study of optic gliomas. They described their material as showing "a recognizable anterior extension of the pituitary fossa which passes like the neck of a gourd under the anterior clinoid process. This is demarcated from the sella proper by the elevation made by the olivary eminence or tuberculum sellae." Anatomically, there cannot be an anterior extension of the pituitary fossa if the tuberculum sellae is present (Fig. 17, *A* and *B*). Analy-

sis of their material shows the tuberculum sellae to be present in 5 of the 7 presented cases (Cases 1, 2, 3 and 6). As will be discussed in a later section dealing with optic gliomas, Martin and Cushing were correct in their analysis of the anatomic components of their abnormal roentgenograms. However, their descriptive term, which has persisted in the literature, did not apply to their roentgenographic material.

B. THE VALIDITY OF SELLAR DESCRIPTIVE TERMS

Much of the present difficulties in the assessment of the infantile sphenoid have resulted from the uncritical use of the terms such as the J or omega-shaped sella. Certain abnormal cases demonstrate an absent tuberculum sellae. In these cases (Fig. 12, *A–D*) the sellar floor is continuous with a depressed or eroded chiasmatic sulcus. The term "J shaped" sella introduced by Davidoff and Epstein[7] can be used to describe this type of presellar sphenoid as it simulates the letter J lying on its side (Fig. 12*D*). It should be noted that the roentgenogram to which Davidoff and Epstein originally applied this term demonstrates tuberculum sellae and chiasmatic sulcus erosion. The term omega-shaped sella[6,15,19] could be used to describe cases of isolated true excavation of the chiasmatic sulcus (Fig. 14*B*). If one insists on using these terms it is important to note that (a) these terms *do not* apply to the normal presellar sphenoid and (b) each term describes different pathologic features. These distinctions have not been applied in the literature.

Summarizing the descriptive aspects of the past literature, it appears that: (1) some normal roentgenographic structures have been described as abnormal; (2) certain descriptions have implied the presence



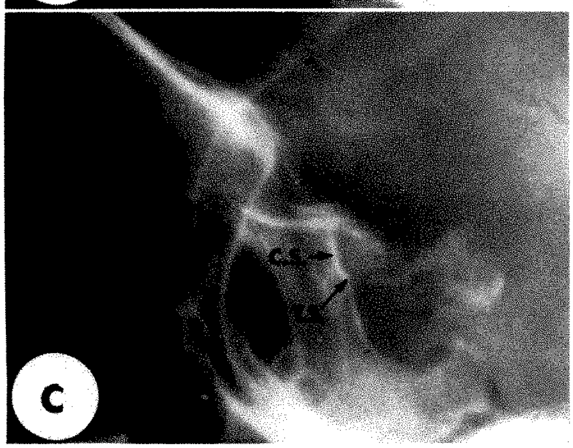


Fig. 9. Roentgenograms demonstrating erosion of tuberculum sellae in the infantile sphenoid. (*A*) Pontine glioma case showing a distinct tuberculum sellae (T. S.) at age 4 years. (*B*) Same case at age $6\frac{1}{2}$ years. The tuberculum sellae has been eroded. (*C*) A 2 year old craniopharyngioma case showing tuberculum sellae erosion. The erosion may be difficult to appreciate as the normal tuberculum sellae may be quite small in this type of presellar configuration (see Figure 8*B*).

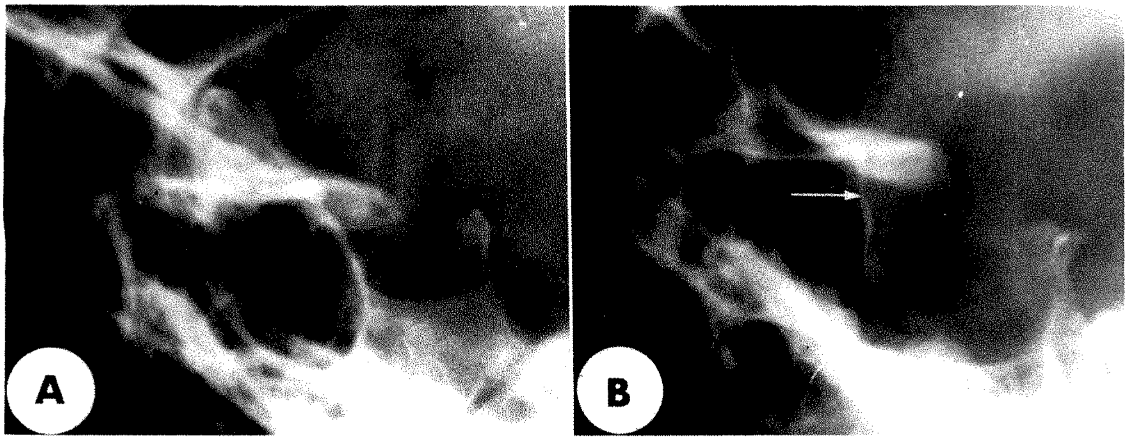


Fig. 10. Case of cerebellar astrocytoma demonstrating resistance to destruction of the pneumatized tuberculum sellae region. (*A*) At age 10 years. Loss of sharp outline of floor and dorsum of sella is noted. (*B*) At age 18 years. Marked destruction of the sellar floor is present. Note that the region of the pneumatized tuberculum sellae (arrow) is intact.

of abnormalities which are not present in the roentgenograms; and (3) descriptive terms such as the J shaped sella have been used to describe both normal and abnormal features. These problems have resulted from the lack of precise anatomic definition of the presented roentgenograms. When specific anatomic descriptions such as "eroded chiasmatic sulcus"[20] and "atrophy or underdevelopment of the tuberculum sellae"[11] are used, the descriptive roentgenographic correlation has been precise.

The replacement of the terms such as the J or omega-shaped sella by anatomic descriptions would greatly simplify the assessment of the infantile sella. These terms, however, appear to be well entrenched. A more precise and anatomically correlated use of these terms would greatly enhance their clinical significance.

C. INCIDENCE OF PRESELLAR ABNORMALITIES

The abnormal material in this study and in the previous literature was evaluated to

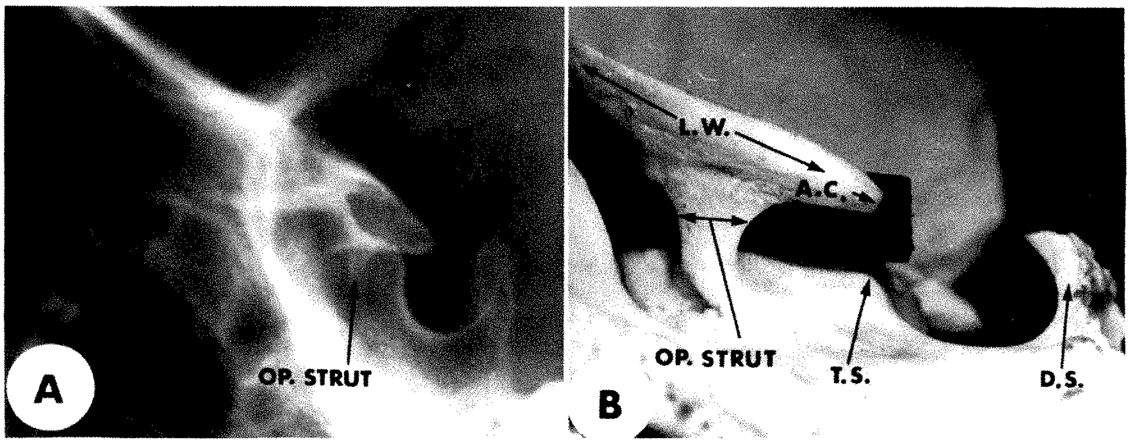


Fig. 11. The optic strut in normal lateral skull roentgenograms. (*A*) Normally the optic strut is seen only faintly *through* the chiasmatic sulcus. (*B*) Lateral aspect of sphenoid specimen in position simulating a lateral skull roentgenogram. The optic strut is the inferior root of the lesser sphenoidal wing (L. W.). The tuberculum sellae (T. S.) and chiasmatic sulcus are partially obscured by the black marker simulating the optic nerve. A. C. = anterior clinoid; D. S. = dorsum sellae.

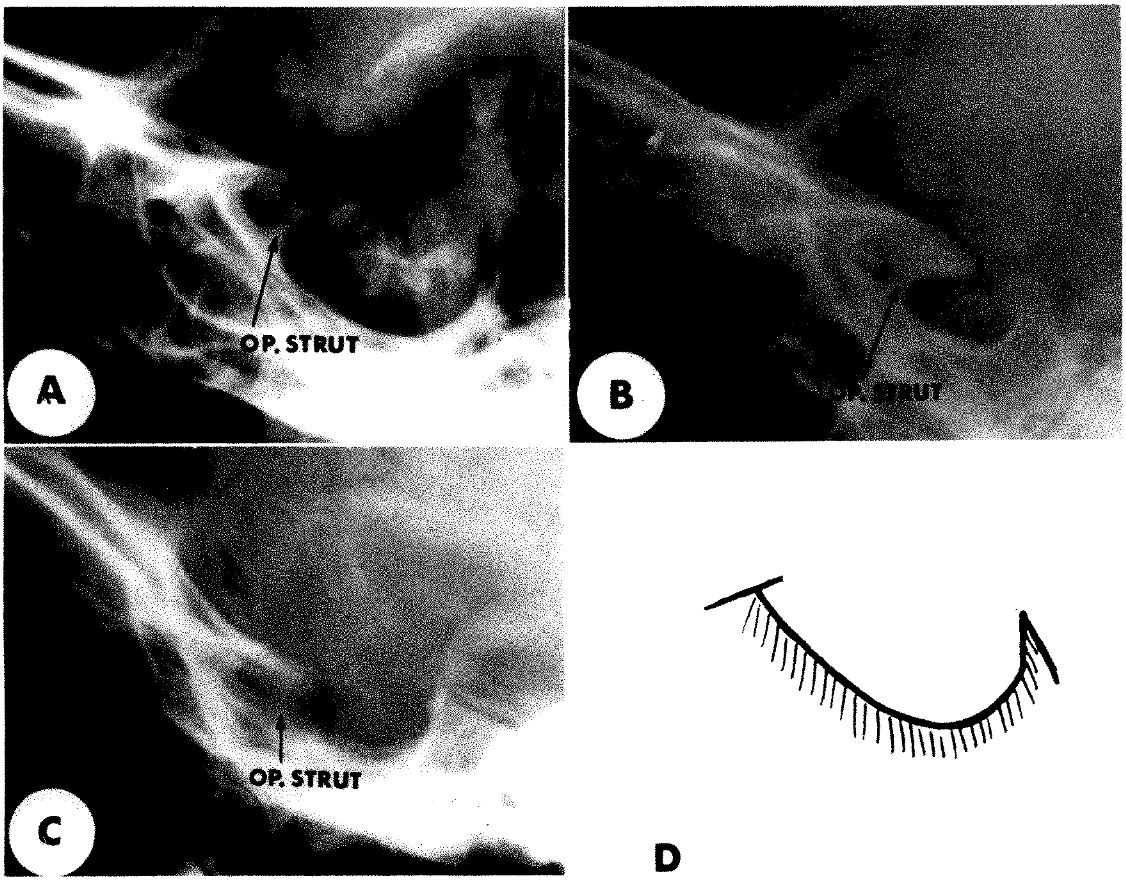


FIG. 12. The optic strut in abnormal lateral skull roentgenograms. (*A*) A 7 year old craniopharyngioma case. (*B*) A 5 year old craniopharyngioma case. (*C*) An 8 year old case with a parasellar subarachnoid cyst. Note the clear visualization of the optic strut in these cases. This phenomenon is only possible in the presence of tuberculum sellae and chiasmatic sulcus flattening or erosion. It is not present in normal cases. The optic strut *should not* be mistaken for the tuberculum sellae thus implying a lesser destructive process than is actually present. (*D*) Tracing of case in *A* demonstrating absence of the anterior sellar wall.

determine the incidence of presellar abnormalities. The following conditions were investigated:

(*1*) *Craniopharyngioma.* Twenty-five surgically proven cases were reviewed. Nine of the 10 cases with infantile sphenoids demonstrated either isolated tuberculum sellae erosion (Fig. 9*C*) or combined tuberculum sellae and chiasmatic sulcus erosion (Fig. 12, *A* and *B*). Two children with adult sphenoids showed similar abnormalities. Ten adult cases showed no presellar abnormalities.

In 3 adult cases the presellar region could not be evaluated because of total destruction. Presellar abnormalities were present in the cases with infantile sphenoid presented by Hertz and Rosendal[20] and other authors.[2,27] Presellar abnormalities were rare in Hertz and Rosendal's infants with adult sphenoids or in the adult material presented in the literature.[2,9,27,40] It appears that presellar abnormalities are a frequent feature of craniopharyngioma presenting in cases with infantile sphenoids.

(*2*) *Optic glioma.* Review of the literature reveals that the roentgenographic evaluation of the sella and presellar sphenoid has been most controversial in this condition. The literature includes a number of optic glioma cases with roentgenographically normal presellar sphenoids, which

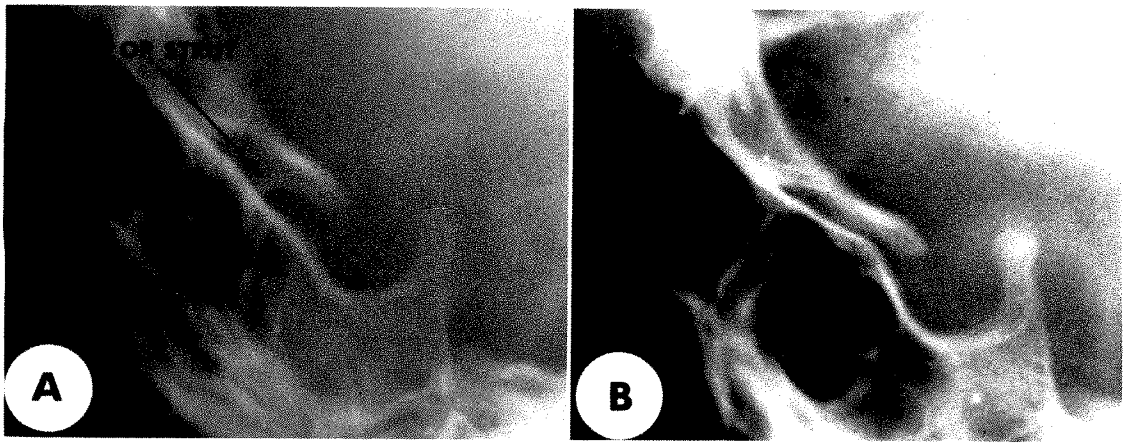


Fig. 13. Case of arrested hydrocephalus demonstrating masking of an abnormal presellar sphenoid by the development of the sinus. (*A*) At age 6 years. Note the abnormal configuration with visualization of the optic strut. (*B*) At age 13 years. Pneumatization of the sphenoid has restored the normal presellar configuration. The optic strut is not seen.

are interpreted as abnormal. Martin and Cushing[30] were the first to draw attention to the roentgenographic appearance of the presellar sphenoid in cases of optic glioma. As a result of their paper and its interpretation by others, roentgenographic chiasmatic abnormalities have been overemphasized and overdiagnosed in the literature. However, a normal presellar sphenoid may frequently be present in early cases of chiasmatic or optic nerve gliomas. This is a result of the following anatomic features: (a) Schaeffer[37] in his dissection of 125 cadavers noted that the optic chiasm was located on the dorsum sellae or the diaphragma sellae in 95 per cent, and over the chiasmatic sulcus in only 5 per cent of his cases. Similar findings were noted in a recent study[3] of 225 autopsies. Thus, presellar abnormalities may not be present in early lesions of the optic chiasm because of the chiasm's frequent posterior location. (b) Martin and Cushing's surgical illustration (Fig. 17*B*) clearly demonstrates the sparing of the chiasmatic sulcus and tuberculum sellae by a tumor within the cranial opening of the optic canal. In this situation the only roentgenographic abnormality will be the presence of an elevated optic canal roof (Fig. 17*A*). (c) In cases with small tumors, a pathologic upward displacement of the optic canal roof will not be detected roentgenographically because of the normally superior position of the roof during early infancy.

The wide variability in the appearance of the presellar sphenoid in optic glioma cases, which was pointed out by Holman,[21] can be explained by the location and size of the tumor. Thus the presenting roentgenographic features will vary and may show marked presellar destruction,[4,20] presellar erosion or flattening,[6,7,13,20,31,40,41] elevation of the optic canal roof[30,40] or no abnormal changes.[20,21,27] This study's material included 4 cases of optic glioma in infantile sphenoid. Three of these showed no abnormalities in the lateral roentgenogram.

Martin and Cushing[30] repeatedly stressed that the abnormalities present in their roentgenographic material were most likely due to "dilated optic foramina." Goalwin[16] erroneously interpreted their material as showing "a deepened and enlarged sulcus chiasmaticus." It appears that Goalwin's interpretation has contributed to the persistence of overinterpreted cases presented in the literature. It should also be noted that Martin and Cushing did not use the term "J sella." This term does not apply to their material as the tuberculum sellae is present and was described as such in the

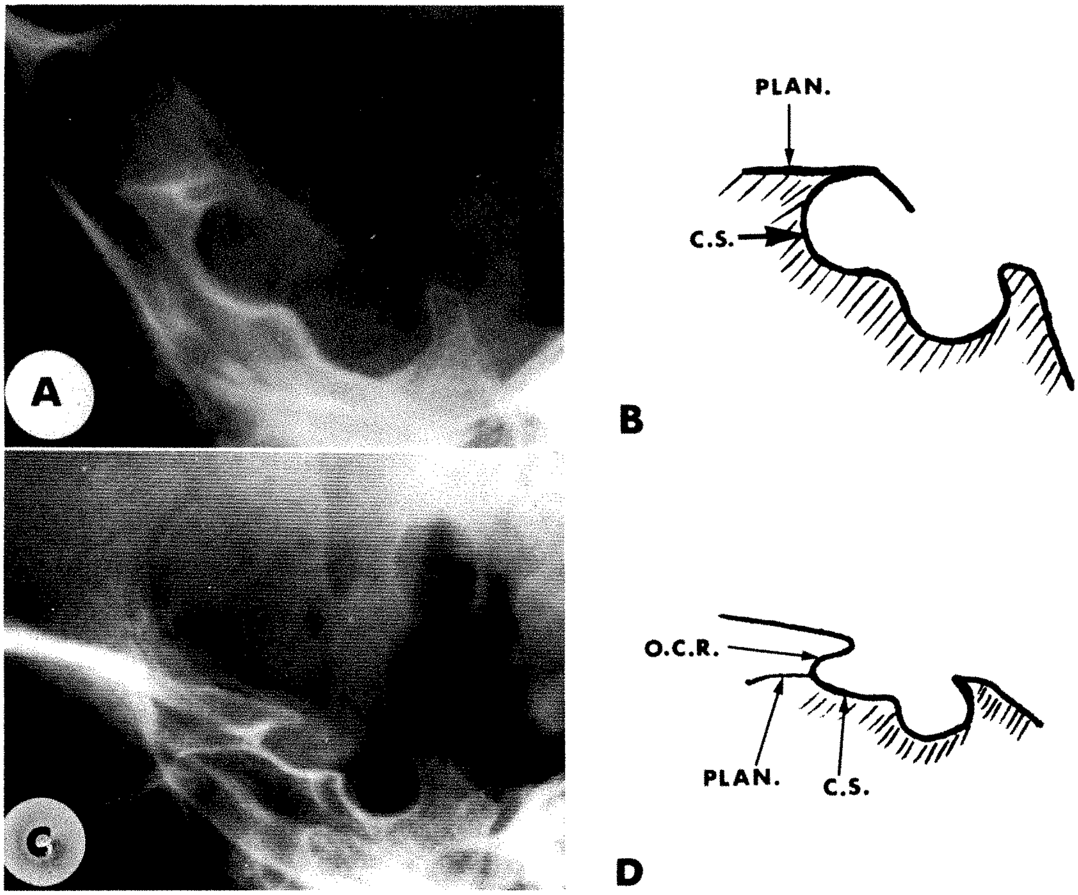
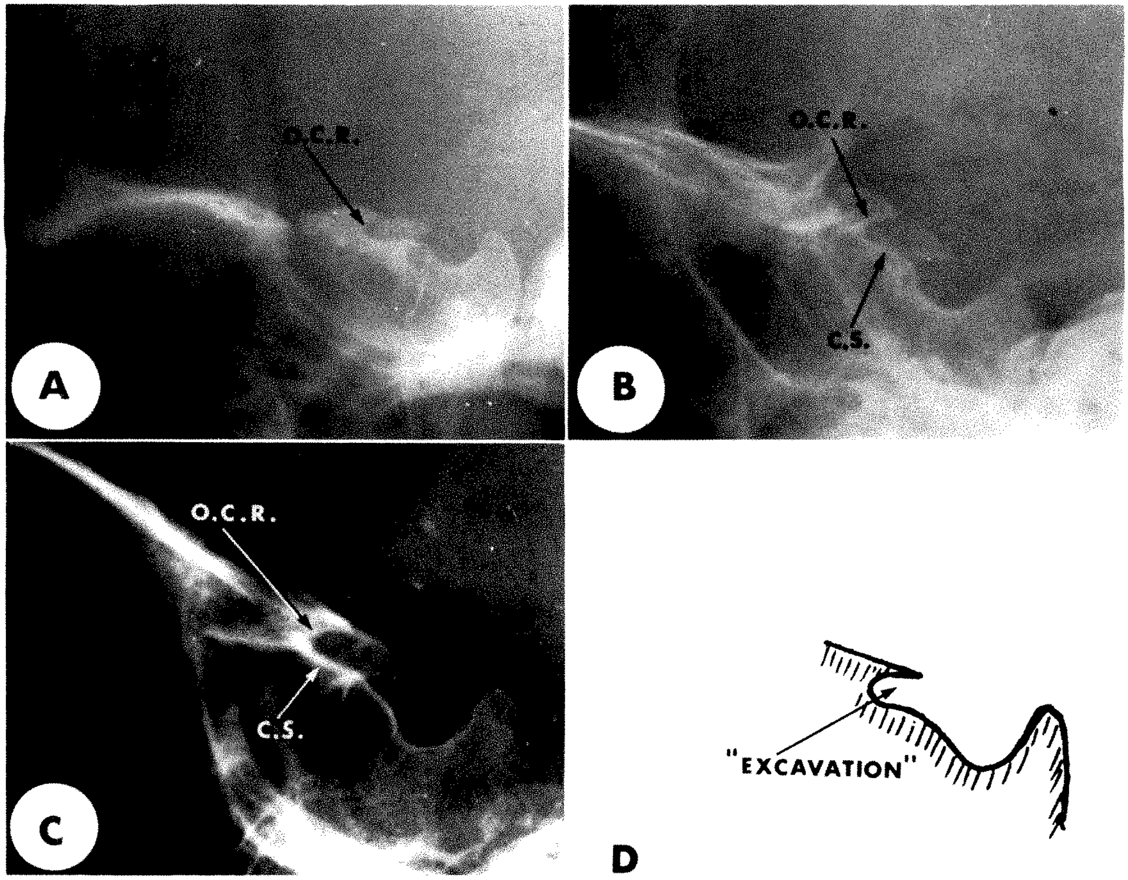


Fig. 14. True *versus* false excavation of the chiasmatic sulcus. (*A* and *B*) A 3 year old case of optic glioma with neurofibromatosis. Note the excavation of the chiasmatic sulcus (C. S.) below the level of the planum sphenoidale (PLAN.). (*C* and *D*) A 2 year old with normal presellar sphenoid. Note that the normal chiasmatic sulcus is continuous with the planum sphenoidale. The prominent optic canal roof (O. C. R.) *should not* be incorporated into a false diagnosis of chiasmatic sulcus excavation.

majority of their cases.

(*3*) *Posterior fossa tumors.* Fifteen cases of posterior fossa tumors with infantile sphenoids and normal head size were evaluated in this study. Only one case (Fig. 9, *A* and *B*) showed an abnormal presellar sphenoid. Review of the many cases presented in the literature reveals rare instances of presellar abnormalities. Hertz and Rosendal[20] did not list posterior fossa tumors as a cause of tuberculum sellae and chiasmatic sulcus abnormalities. It appears that presellar abnormalities are rarely present in cases of posterior fossa tumors with normal head size and infantile sphenoid.

(*4*) *Hydrocephalus.* Twenty-five cases of increased head size associated with an infantile sphenoid were included in this study. None of these had intracranial tumors or skeletal dysplasias. These cases demonstrated the frequent findings of a poorly defined planum, an elongated chiasmatic sulcus and thin anterior clinoids (Fig. 18, *A*, *B* and *C*). Cases with increasing head size showed an associated flattening of the tuberculum sellae (Fig. 20, *A* and *B*). Three cases with severely enlarged heads showed a completely absent tuberculum sellae. The possible relationship between increasing head size and tuberculum sellae flattening will be discussed in the section



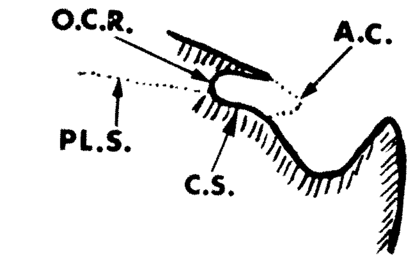


Fig. 15. Elucidation of the mythical "abnormal excavation." (*A*, *B* and *C*) Children with normal presellar sphenoids. These are similar to the cases presented in the literature as showing "excavation under the anterior clinoid process." (*D*) Tracing similar to the ones presented in the literature to illustrate the "abnormal excavation." Note that the so-called excavation is a roentgenologic illusion resulting from the prominence of the optic canal roof (O. C. R.) during infancy. The laterally positioned optic canal roof forms the superior component of the so-called excavation and projects as a dense white line which appears to be continuous with the normal and midline chiasmatic sulcus (C. S.). (*E*) Tracing demonstrating the correct anatomic components of the "excavation." A. C. = anterior clinoid; PL. S. = planum sphenoidale.

dealing with the etiology of presellar abnormalities.

(5) *Mental retardation.* Twenty cases of mental retardation with infantile sphenoids and normal head size were included in the material studied. These showed no abnormal presellar features. Timme[43] claimed that his cases of mongolism showed "excavation under the anterior clinoid process." Review of his presented roentgenograms shows no abnormal presellar sphenoids. Subsequent authors[5,17,38] have not found presellar abnormalities in mongolism.

(6) *Gargoylism.* It is stated that the J

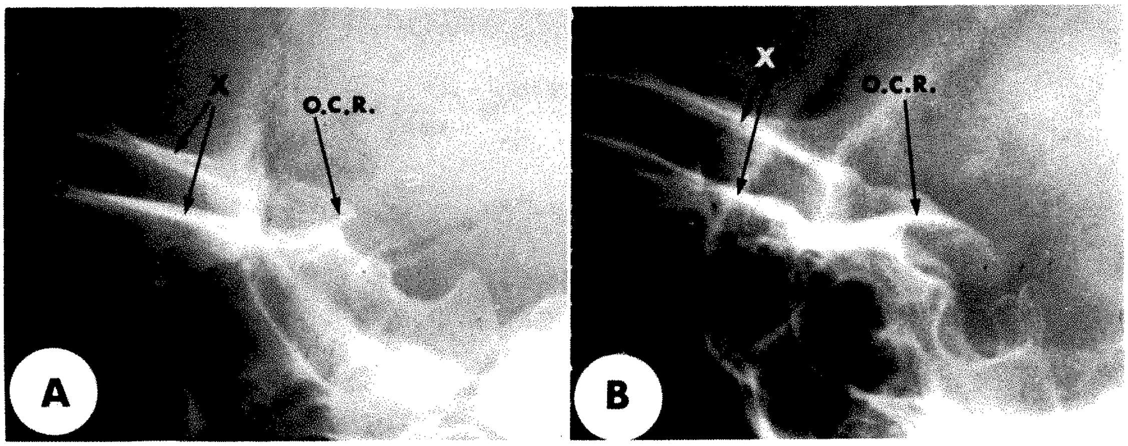


Fig. 16. (*A* and *B*) Children with normal presellar sphenoids. Note that the imperfect (X) lateral roentgenograms markedly accentuate the so-called excavation by further elevation of the laterally positioned optic canal roof (O. C. R.).

shaped sella is a feature in gargoylism.[22] The material of this study included 3 cases of gargoylism with infantile sphenoids. These cases had normal head size and showed no presellar abnormalities (Fig. 19). The only gargoylism cases presented in the literature which demonstrate an absent tuberculum sellae and depressed chiasmatic sulcus are cases with an increased head size.[4,12,22,31,41] It is probable that the abnormal presellar sphenoid is a feature of the increased head size, rather than of the gargoylism itself. This has been alluded to by Taveras[41] and will be discussed further in the section dealing with etiologies of presellar abnormalities.

(7) *Skeletal dysplasias.* Nine cases of various skeletal dysplasias with infantile sphenoid were included in this study. None

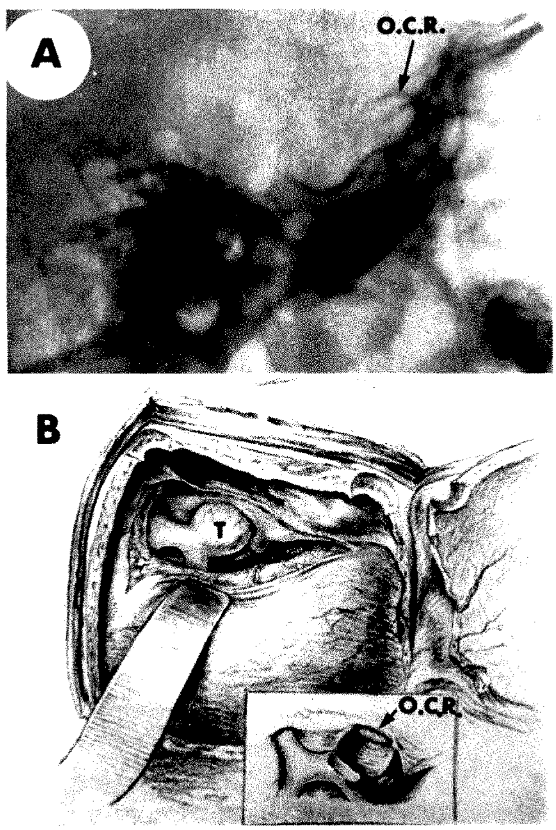


Fig. 17. The genesis of some current misconceptions. (*A*) This roentgenogram reproduced from Martin and Cushing's optic glioma article demonstrates an infantile sphenoid with no abnormalities except for an elevated optic canal roof (O.C.R.). The anterior sellar wall is intact. Thus their description of an "anterior extension of the sella" is inappropriate. This descriptive term has persisted in the literature and has been applied to normal infantile sphenoids. (*B*) Surgical illustration reproduced from the same paper demonstrates sparing of the tuberculum sellae and chiasmatic sulcus by a tumor (T) within the cranial opening of the optic canal. Goalwin's overinterpretation of their material as showing a "deepened and enlarged chiasmatic sulcus" has persisted in the literature. (Reproduced by permission from *Archives of Ophthalmology*, 1923, *52*, 209–241. Arrows, [O.C.R.] and [T] added by present author.)

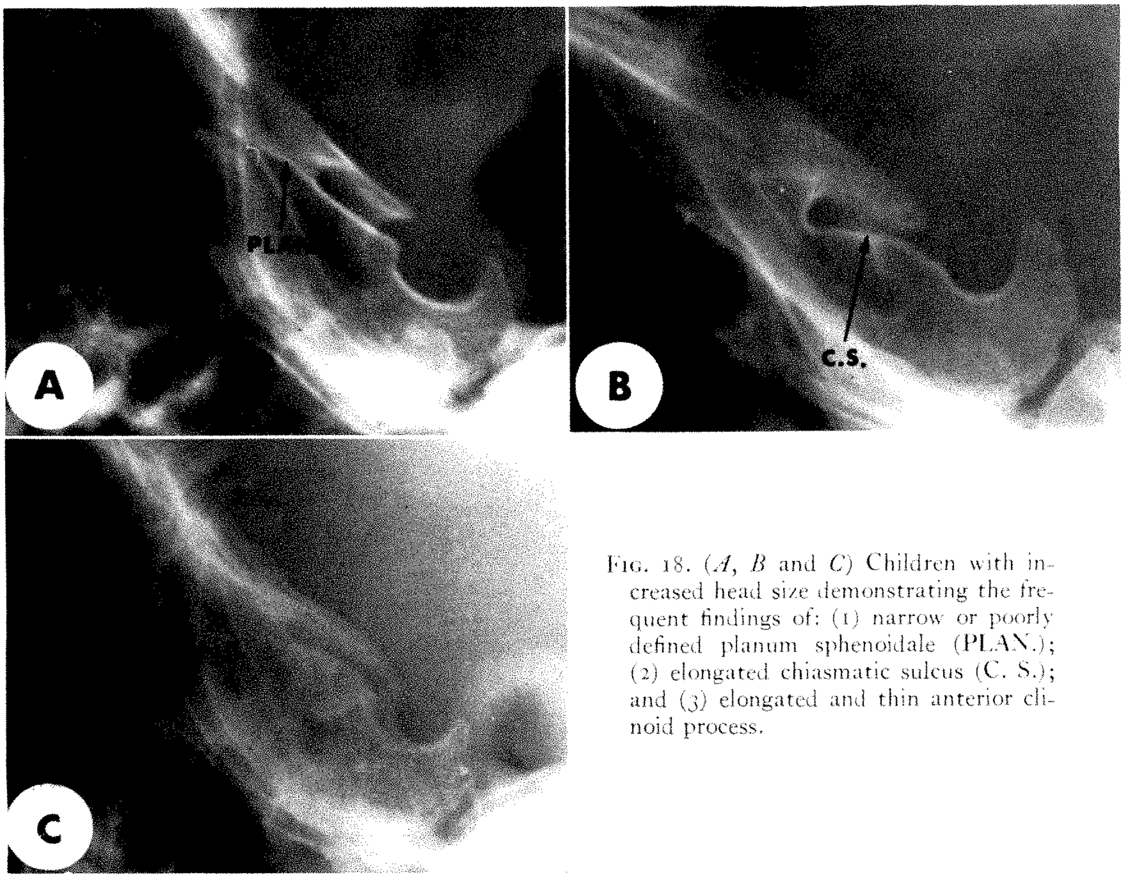


Fig. 18. (*A*, *B* and *C*) Children with increased head size demonstrating the frequent findings of: (1) narrow or poorly defined planum sphenoidale (PLAN.); (2) elongated chiasmatic sulcus (C. S.); and (3) elongated and thin anterior clinoid process.

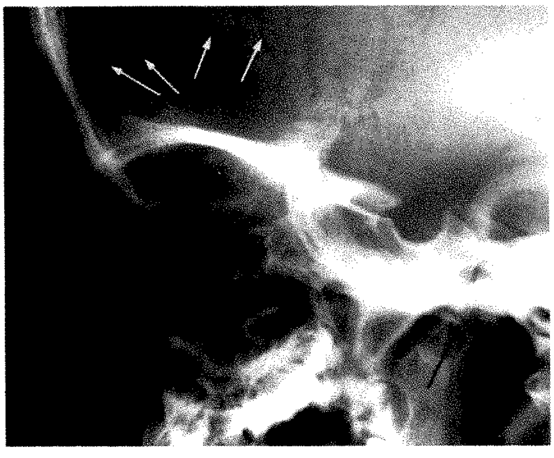


Fig. 19. The overinterpreted sella in gargoylism. This 2 year old gargoylism case with normal head size demonstrates the typical frontal and mandibular features (arrows). The presellar sphenoid, however, is normal. The statement in the literature that an abnormal presellar sphenoid is a constant finding in gargoylism should be restricted to cases with increased head size.

showed an abnormal presellar sphenoid. Although these conditions are mentioned[4,21,33] as demonstrating J shaped sellae, no roentgenograms are presented for evaluation, except for the case presented by New.[33] The latter case had associated hydrocephalus and the appearance of the presellar sphenoid could be a result of the hydrocephalus.

(*8*) *Neurofibromatosis*. The infantile sphenoid material evaluated included only 2 cases of neurofibromatosis. One had a normal presellar sphenoid. The other is presented in Figure 14*A*. Because of the association of neurofibromatosis with optic gliomas, the discussion regarding the roentgenographic features of optic glioma applies also to neurofibromatosis.

D. THE ETIOLOGY OF PRESELLAR ABNORMALITIES

The following etiologies were reviewed:

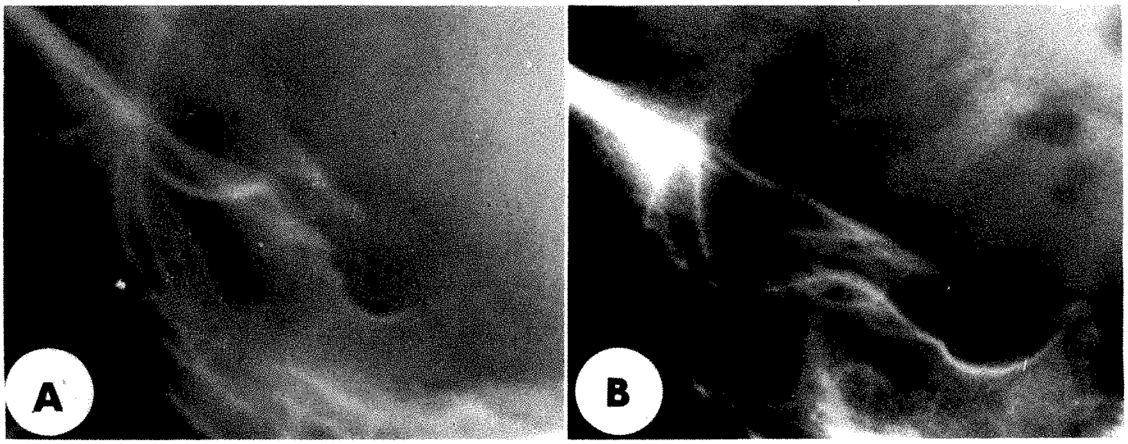


FIG. 20. A case of hydrocephalus demonstrating presellar flattening with increasing head size. (*A*) At age 1 year. Occipitofrontal diameter is 21 cm. (*B*) At age 2 years. Occipitofrontal diameter is 26 cm. Note the flattening of the presellar sphenoid in *B*.

(*a*) *Suprasphenoidal masses.* Dyke,[11] Davidoff and Epstein[7] and Holman[21] have postulated that presellar abnormalities in optic gliomas result from the presence of a tumor mass preventing or deforming the normal sphenoid development in the perinatal period. The present study supports this theory. The region of the tuberculum sellae and chiasmatic sulcus ossifies late in fetal life and may be quite fragile in the postnatal period. Thus deformity of the ossifying cartilage by a prenatal tumor and compression or erosion of this region by a postnatal mass is a valid assumption.

(*b*) *Raised intracranial pressure.* This study's material and review of the literature reveal only rare instances of true presellar abnormalities in cases of posterior fossa tumors with normal head size. Du Boulay and El Gammal's review[10] of sellar changes in raised intracranial pressure does not stress presellar changes. The present study did find, however, increased tuberculum sellae flattening with increasing head size. It is postulated, therefore, that the presence of tuberculum sellae flattening in hydrocephalus with increased head size, is not the result of increased intracranial pressure but may be due to stretching of the base of the skull. This would explain the rarity of presellar abnormalities in posterior fossa tumors with increased intracranial pressure but normal head size. It may also explain the presence of abnormal presellar sphenoids in gargoylism only when the latter condition is associated with increased head size. The presence of some sellar abnormalities in gargoylism has been elucidated by a recent study[32] which demonstrated the presence of large intrasellar subarachnoid cysts in several cases of gargoylism. This new report reinforces the importance of suprasphenoidal masses as a cause of presellar abnormalities.

(*c*) *Developmental defect.* Burrows[4] has postulated that the J shaped sella may be the result of defective cartilaginous growth at the region of the intersphenoid synchondrosis. The present study does not substantiate this postulate. The intrasphenoid cartilage is usually well ossified at birth, especially at the superior surface of the sphenoid. The normal notch between the limbus sphenoidalis and the underlying sphenoid should not be mistaken for a persistent intersphenoid synchondrosis.

SUMMARY AND CONCLUSIONS

A developmental study of the sphenoid was undertaken to provide objective criteria for the assessment of the infantile sella turcica. The past literature was reappraised regarding the validity of pre-

viously presented descriptions, definitions and etiologies of sellar abnormalities in infancy.

The developmental anatomy of the superior surface of the sphenoid anterior to the floor of the sella was investigated anatomically and roentgenologically. The material consisted of: (a) 26 cleared and alizarin stained fetuses, 45 dissected fetal sphenoids, 18 dissected infant sphenoids, and 100 sphenoids examined in dry adult skulls; and (b) lateral skull roentgenograms of 50 fetuses, 200 normal newborns, 100 normal infants, 100 normal adults, 50 adults with sellar abnormalities and 85 infants with abnormalities. All the infant roentgenologic material had a partially developed sphenoid sinus.

This study has correlated the developmental anatomy of the presellar sphenoid with its roentgenologic manifestations. In addition, the following diagnostically significant points have been elucidated:

(1) Pathologic changes of the presellar region (tuberculum sellae, chiasmatic sulcus, planum sphenoidale and optic canal roof) are distinct from normal growth patterns.

(2) Improper lateral skull roentgenograms may produce "abnormal" presellar features.

(3) Presellar abnormalities may be masked, distorted or retarded by a developing sphenoid sinus.

(4) Many of the reported cases demonstrating an "abnormal sella turcica" only show normal developmental patterns.

(5) Only very few pathologic conditions present abnormal presellar features.

(6) Descriptive terms such as the J or omega-shaped sella can be restricted to abnormal infantile sphenoids.

(7) The presence of presellar abnormalities in suprasellar masses of early infancy result from erosion or pressure deformity of the late ossifying tuberculum sellae rather than defective cartilaginous growth.

(8) It is postulated that some presellar abnormalities in pathologic conditions with marked increase in head size may result from stretching and thinning of the base of the skull.

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THE LATERAL COMPRESSION ROENTGENOGRAM OF THE ABDOMEN IN PREGNANCY*

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LATERAL roentgenograms of the pregnant abdomen are valuable for a variety of purposes and have certain advantages over anteroposterior, posteroanterior and oblique views. In the lateral study the fetus is seen to be relatively free from maternal bony structures and distracting gas and fecal shadows in the maternal bowel. For these reasons the lateral roentgenogram, ordinarily made with the patient recumbent, has been used to search for fetal abnormalities, to determine the presence of more than one fetus, to locate the placenta, to seek signs of fetal maturity or fetal death, and to determine fetal position prior to intrauterine transfusion. The lateral roentgenogram has value following the injection of contrast material into the abdominal aorta for localization of the placenta[3] and may offer advantages in placental localization following opacification of the amniotic fluid.[4]

METHOD

Certain technical problems must be overcome to obtain high quality lateral roentgenograms of the abdomen. Since the amount of tissue to be penetrated is much greater posteriorly than anteriorly, films exposed without regard for this difference will be underpenetrated in the region of the posterior part of the uterus and overexposed near the maternal umbilicus. Several ways of overcoming this disadvantage have been suggested, and all have certain virtues. Bishop[1] described the use of a special cassette containing two sets of screens of different speeds. The cassette is loaded with 2 films, and they are exposed simultaneously from 1 roentgen-ray exposure. One film is more heavily exposed (darker) and shows the posterior part of the uterine contents to advantage, while the other is lighter and shows the anterior part. Another corrective method employs the use of wedge filters at the tube head to compensate for the differences in thickness. Yet another technique involves compression of the abdomen from side to side with a cloth band, but this does little to equalize densities.

All of these methods have advantages, and high quality roentgenograms may be produced using each of these techniques. In all of them, an effort is made to obtain a reasonably good view of the entire maternal abdomen and contents of the uterus, and, while this is often helpful and occasionally necessary, it is done at the sacrifice of detail as regards the fetal parts. When interest centers primarily in the fetus, as for example in the prediction of fetal age and maturity, a different approach may be more suitable. We have used a device which compresses the maternal abdomen anterior and inferior to the rib margins and anterior to the pelvis. Its purpose is to immobilize the fetus, diminish the thickness of the uterus and render all parts of the uterus and maternal abdomen of relatively equal thickness so that a film may be exposed which will show all parts of the compressed abdomen and uterus with equal clarity and density. Such a device is illustrated in Figure 1, *A* and *B*, and a table of exposure factors for various thicknesses of the abdomen (measured from the top to the bottom of the plexiglass plates) is presented in Table 1. While this device is of our own design, the idea is not original. Similar devices are in use in Sweden and doubtless elsewhere.

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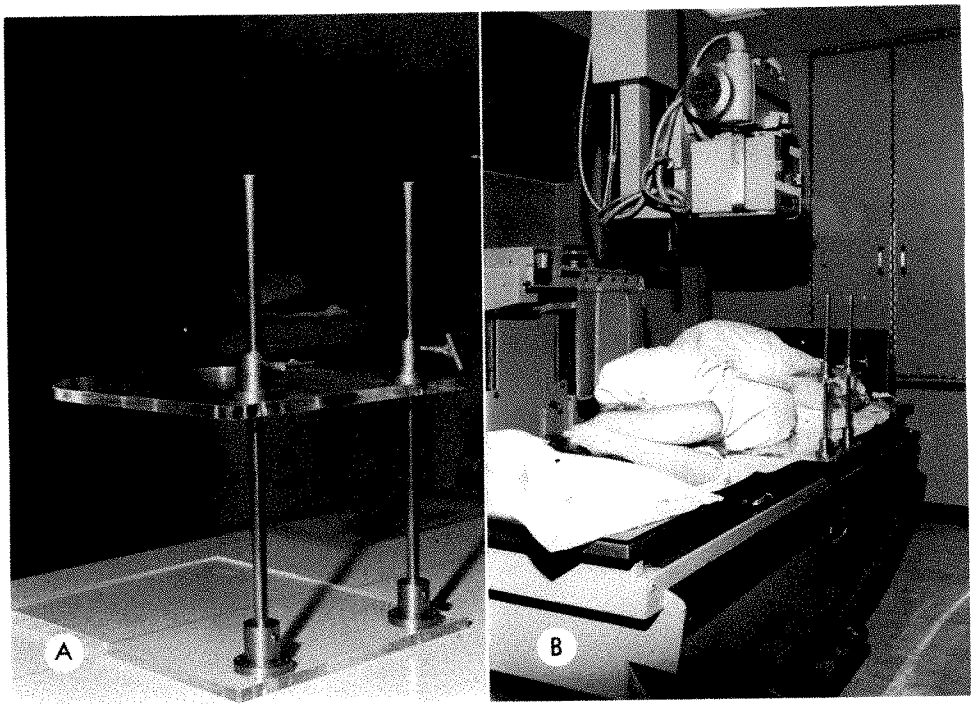

Fig. 1. (*A*) The mechanical compression device is homemade, built of steel, brass and plexiglass. The upper plate has rounded margins to fit the contours of the rib and pelvic margins of the mother. (*B*) The upper plate is lowered until the abdomen is tightly but not painfully compressed.

The advantages of using such a device are as follows: the fetal parts located in the fundus and body of the uterus are seen with great clarity, and the distal femoral and proximal tibial epiphyseal ossification centers can ordinarily be sought and found with ease if present; the fetal fat line is well seen, and its degree of development can be appraised; the fetal lumbar spine is ordinarily well shown, and it can be measured in an attempt to estimate the length of the fetus;[2] an over-all estimate of the size of the fetus is possible, allowing one to make a reasoned guess of the fetal weight. An unexpected extra advantage has been the remarkably clear demonstration of the implantation site of the placenta in a large percentage of cases. The disadvantages of the use of the device include the following: in a cephalic presentation, the head of the fetus is poorly seen; in a breech presentation the fetal lumbar spine and knees may be poorly seen; when the fetus is very small and lies largely within the maternal pelvis the lateral compression view may show little if anything of value.

RESULTS

The findings in the last 50 consecutive patients examined by this technique were

Table I

EXPOSURE FACTORS* FOR VARIOUS THICKNESSES OF THE ABDOMEN

cm.	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
kvp.	65	67	69	71	73	75	77	79	81	83	85	89	92	95	98	101

* Exposure factors for use with the compression device at 40 inches target-to-film distance, using par speed film, high speed screens and a 16:1 grid in a Potter-Bucky diaphragm. All films are exposed at 30 mas. using the fastest possible time. Kilovoltage is determined from the above chart depending upon the distance in cm. from the tabletop to the top of the upper plate of the compression device. Included in the kilovoltage figures is allowance for the grid and for the fact that the beam is collimated. The central ray is directed at the most posterior part of the *compressed* abdomen.

evaluated. The authors examined the roentgenograms separately, and their results were tabulated and are summarized here. Thirty-two of the patients' babies were delivered within 7 days of the exposure of the film, and these form the substance of this analysis.

FETAL MATURITY

Twenty-eight of the infants were judged to be mature and 4 premature on the basis of birth weight and clinical examination. Criteria for the roentgenologic estimation of maturity included the following: presence or absence of the epiphyseal ossification centers about the knee; presence and extent of development of the fetal fat line; length of the fetal lumbar spine; development of the fetal skeleton with regard to the thickness of the long and skull bones in particular; and an over-all impression of the size of the infant on subjective grounds. The 4 premature infants were judged to be premature on the basis of the roentgenographic findings by both examiners. Twenty-seven of the 28 infants thought to be clinically mature were considered mature roentgenologically by each examiner. Each examiner thought 1 infant to be premature by roentgenologic criteria, who proved to be mature clinically both by subjective evaluation and birth weight. Thus, in over-all estimation of fetal maturity there was no case in which an infant was thought to be mature roentgenologically and proved to be premature in fact. In one case each, the examiners underestimated fetal maturity.

The degree of development of the fetal fat line was of only occasional value in estimating the degree of fetal maturity (Fig. 2). However, in 4 cases both examiners found the fetal fat line to be absent, and in all 4 the infant was premature at birth. In no case was the infant found to be premature at birth when epiphyseal ossification centers about the knee were roentgenologically visible (Fig. 3, *A* and *B*).

BIRTH WEIGHT

Fetal birth weight was both over and underestimated by both examiners. The average error of estimation of birth weight for each examiner was 11 oz. (range 0–44 oz.). In no case did roentgenologic overestimation of the birth weight lead to a roentgenologic impression of maturity when the infant was in fact premature at birth.

FETAL LENGTH

Estimation of the crown-heel length of the fetus from measurement of the length of the lumbar spine according to the method of Fagerberg and Ronema[2] was possible in 26 patients in whom this figure could be compared with the actual length of the fetus at delivery (Fig. 4). The average error of each examiner in estimating the length of the fetus at birth from the measured length of the lumbar spine was 1.9 cm. (range 0–6 cm.). The length of the fetus was both underestimated and overestimated, although most of the time it was underestimated.

Fig. 2. The fetal fat line is seen with great clarity. Also note the anterior location of the placenta (the mother is facing to the observer's left).

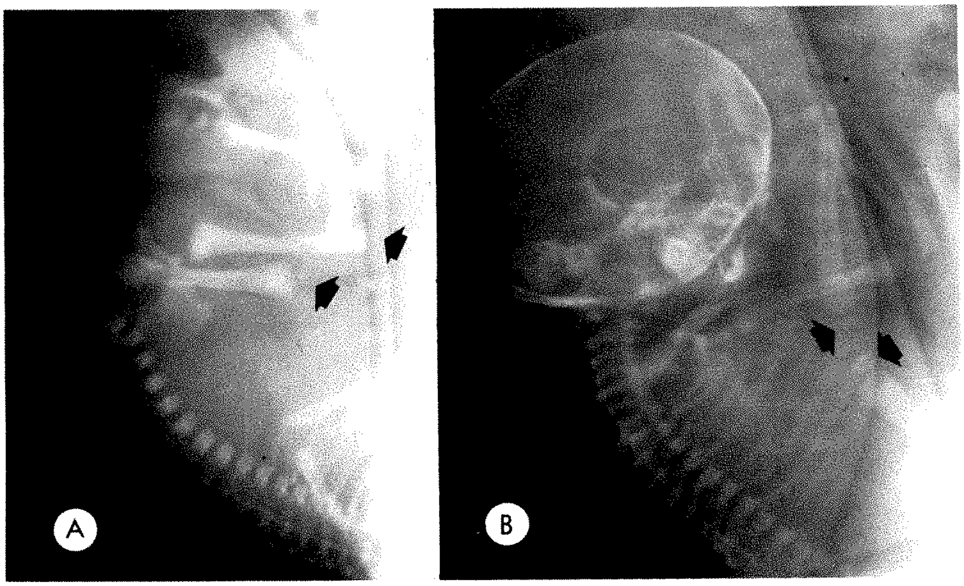

Fig. 3. (*A*) The distal femoral epiphyseal ossification centers are clearly visible (arrows) in this fetus presenting by the vertex. (*B*) The distal femoral and proximal tibial epiphyseal ossification centers (arrows) are clearly visible in this fetus presenting by the breech.

PLACENTAL LOCALIZATION

The placental site was localized in 27 of the 32 patients by the two observers. Because of the likelihood that the compression device displaces amniotic fluid with ease, it seems likely that the crescentic soft tissue opacity interposed between the fetus and the uterine wall represents the placenta when it is clearly seen (Fig. 5). Placental localization is certainly not adequate by this technique when the placenta is found to be partly in the pelvis, but when it is clearly and obviously in the fundus or on the anterior or posterior wall of the uterus near the fundus, it seems that placenta previa can be excluded with reasonable accuracy. In this series there was no clear verification of the location of the placenta at delivery or Cesarean section in any of the patients, and the placental localization therefore remains a presumption. However, in no case was the placenta found in the pelvis interfering with delivery from below where it had been clearly localized near the fundus of the uterus.

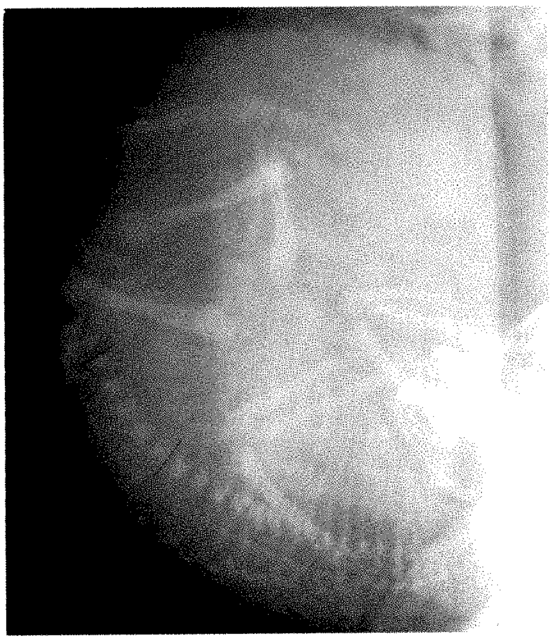

Fig. 4. The length of the fetal lumbar spine can easily be measured in such a roentgenogram and the value obtained used as an aid in the prediction of fetal length according to the method of Fagerberg and Ronema.[2] Also observe the placenta implanted in the fundus posteriorly (the mother is facing the observer's left).

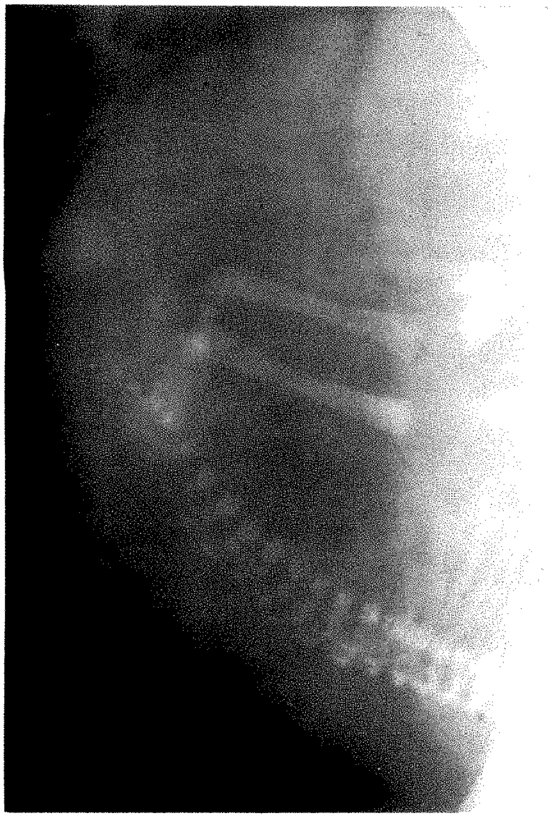

FIG. 5. The placenta is clearly seen as a crescentic soft tissue opacity implanted in the fundus posteriorly (the mother is facing to the observer's left). The fetal lumbar spine could easily be measured on such a roentgenogram as an aid to the prediction of crown-heel length. Distal femoral epiphyseal ossification centers are not seen.

DISCUSSION

We have not made an objective comparison between this method of fetal maturity prediction and any other and cannot, therefore, claim special advantages for this technique. We have been subjectively impressed with the better visualization of the fetus obtained by this method than by any other we have used. Our evidence permits us to claim the ability to estimate fetal birth weight to within about 3/4 of a pound on the average if the infant is delivered within 7 days of the roentgenographic study. Moreover, the method has been sufficiently accurate that we have made no prediction of maturity when the infant proved to be premature, and indeed each observer made only one error in maturity prediction in the series of 32 cases described here. Confirmation of the value of visualization of the distal femoral epiphyseal ossification center as a measure of physiologic maturity was again obtained, and what we suppose to be accurate placental localization was accomplished in about 4/5 of the patients, provided that the placenta was normally implanted. It may be that such a lateral compression roentgenogram would serve well as a preliminary to other forms of placentography and may be adequate by itself when the placenta is clearly implanted in the fundus. In only 2 cases in this series was it necessary to take more than 1 lateral compression roentgenogram in order to obtain the required information.

SUMMARY

A mechanical compression device for use in obtaining roentgenograms of high quality for the examination of the fetus in circumstances where prediction of fetal maturity and age are important is described. Its use largely centers around the prediction of fetal maturity, but it may offer certain distinct advantages in placental localization as well.

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We wish to acknowledge the assistance of Mr. Jim F. Holmes in the conception and design of the compression device.

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LIVER SHUNTS*

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THE vascular alterations of portal cirrhosis have been demonstrated by dissection, injection and digestion cast specimens.[1-6] There has not been agreement of conclusions and much remains unknown about the vascular physiology of the liver in normal and disease states.

Today there is general agreement that the primary site of vascular obstruction in cirrhosis occurs at the distal end of the venous sinusoid or in the proximal hepatic venule. A marked reduction in the size of the venous beds of the hepatic vein is consistently demonstrated. The hepatic arteries show an increase in size, number and tortuosity. The vascular bed of the hepatic artery, when increased, may show a cross-sectional area that may be increased as much as ten times normal. The portal venous channels are not increased in size and may show a slight decrease in caliber but no compression or constriction of the portal venous system is evident.

In advanced portal hypertension due to cirrhosis, portal flow is often reversed. The increased hepatic artery flow that coexists is drained, at least in part, by reversed portal hepatofugal flow. With these altered circulatory dynamics, various vascular shunts are noted with increased frequency and increased magnitude. The shunts consist of: (1) Extrahepatic communications between the portal venous system and the systemic venous system; (2) intrahepatic portal-hepatic venous shunts; and (3) intrahepatic arterial-portal shunts.

The syndrome of portal hypertension encompasses a great variety of pathophysiologic patterns. The most important questions to be answered prior to selecting the appropriate form of treatment and which also serve as a prognostic index are: (1)

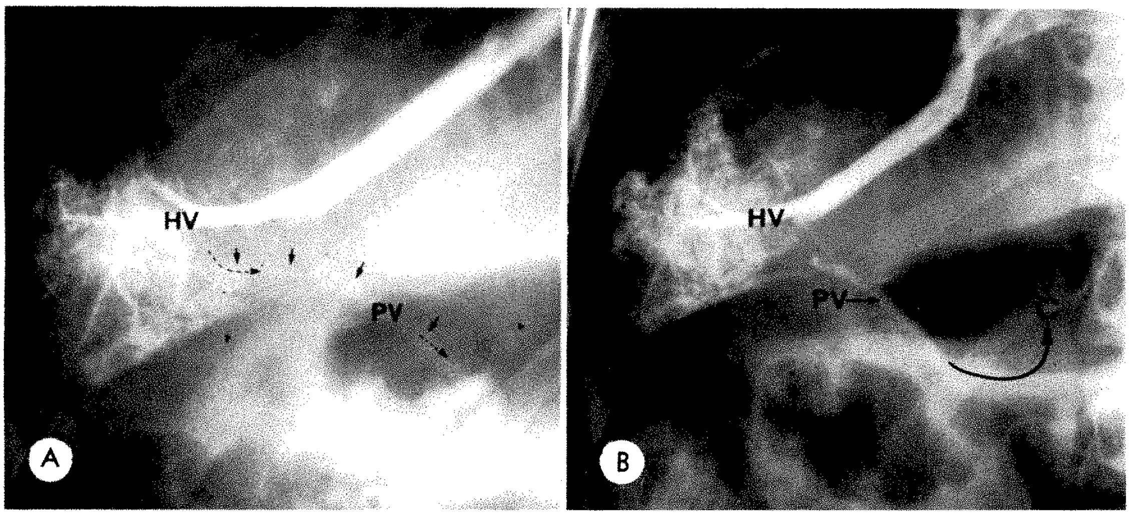

Fig. 1. (*A* and *B*) Wedge hepatic venograms following side-to-side portacaval shunt in a patient with cirrhosis of the liver. Note retrograde opacification (arrows) of the portal vein (PV), which empties into the inferior vena cava (IVC). HV = hepatic vein. Note nonhomogeneous hepatogram.

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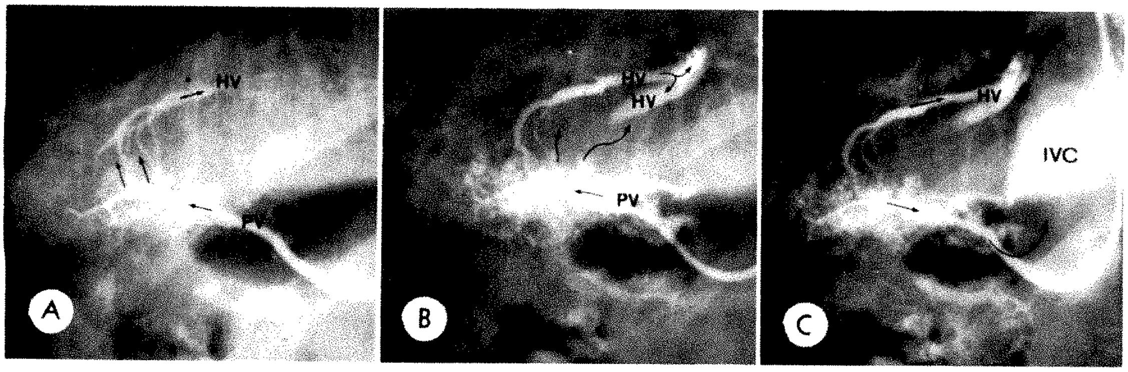

FIG. 2. (*A–C*) Same case as in Figure 1. Direct portograms following percutaneous transfemoral vein catheterization of the inferior vena cava (IVC), and passage of the catheter through the anastomosis into a wedge position in the portal vein (PV).

Degree and activity of liver damage; and (2) altered liver vascular physiology.

Liver damage is assessed by clinical history, physical examination, liver function tests and liver biopsy. Vascular dynamics are studied by: (a) Hepatic vein catheterization (Fig. 1, *A* and *B*; 3; and 5); (b) direct or indirect portography (Fig. 2); (c) hepatic arteriography (Fig. 4; and 6); and (d) estimated total hepatic blood flow determination with radioactive or dye materials.

Volume and distribution of blood to the liver are best assessed by portography and hepatic arteriography. Portography also provides the best information as to the number, location and size of portosystemic collateral veins.

In cirrhotic livers there are frequent minute communications between hepatic arteries and portal veins and between portal and hepatic veins. These shunts are believed to be formed by sinusoid elements that persist after the hepatic cells atrophy and periportal fibrosis develops. Communication between intrahepatic branches of the portal vein and embryologic channels (umbilical and paraumbilical veins) may

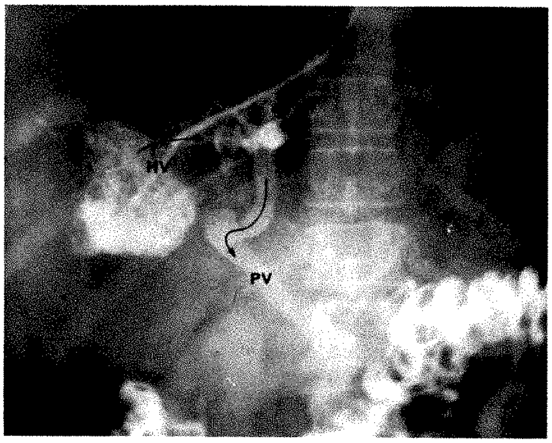

FIG. 3. Wedge hepatic venogram in a patient with cirrhosis of the liver. Note nonhomogeneous, irregular hepatogram. Large channels connect the hepatic vein (HV) with the portal vein (PV). The latter opacifies in a retrograde fashion (arrow); the findings are indicative of a high degree of intrahepatic portal blood flow obstruction. The portal vein trunk and the coronary vein become opacified.

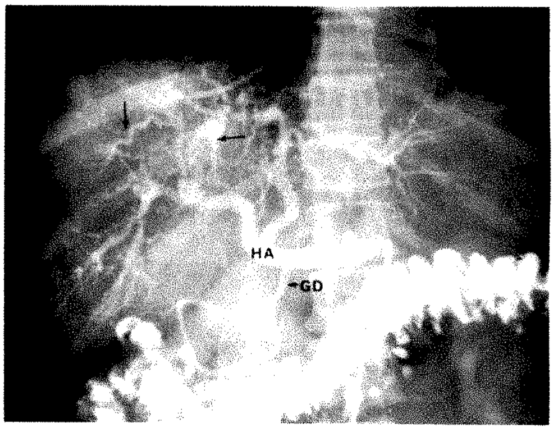

FIG. 4. Same case as in Figure 3. Selective hepatic artery (HA) injection. Hypertrophied, distorted arteries with characteristic spiral course of small intrahepatic arteries, are noted (arrows). GD = gastroduodenal artery. Residual barium is present in the colon.

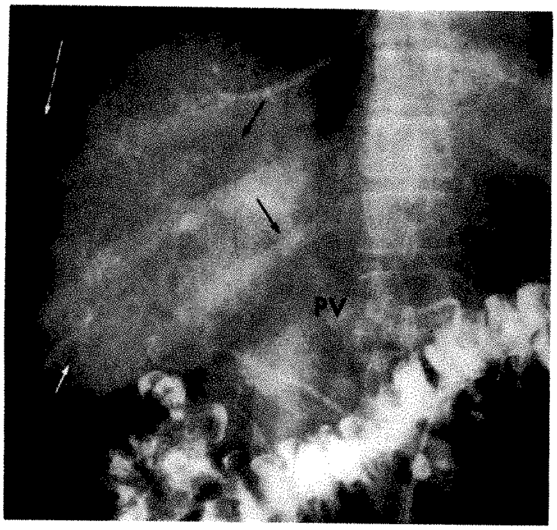

Fig. 5. Same case as in Figures 3 and 4. Hepatogram phase of selective hepatic artery injection. Typical mottled appearance of the liver is observed. There is retrograde visualization (black arrows) of the portal vein (PV). White arrows indicate separation of liver from right flank due to ascites.

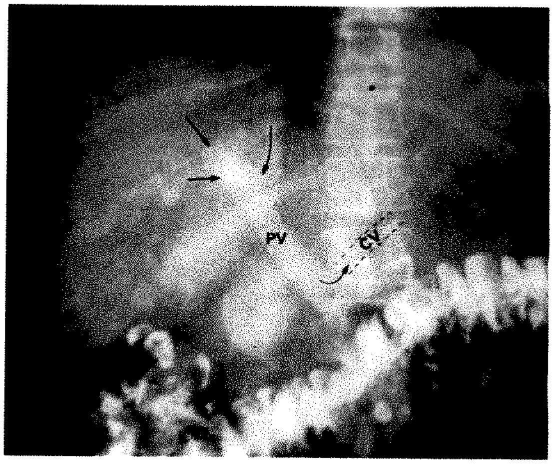

Fig. 6. Same case as in Figures 3, 4, and 5. Late phase of selective hepatic arteriogram. The portal vein (PV) and coronary vein (CV) are remarkably well opacified, secondary to prominent hepatofugal portal blood flow and communication between hepatic arteries and portal veins (arrows).

also be demonstrated, which are enlarged as compensatory shunts between the portal and systemic venous systems.

SUMMARY

Direct or indirect portography has shown the bypass of the liver parenchyma by channels which communicate portal with hepatic venules. Wedge hepatic venography has demonstrated prompt opacification of intrahepatic branches of the portal vein, particularly in patients with reversal of flow in the portal vein. In patients with severe portal hypertension and reversal of flow in the portal vein, one may observe a retrograde visualization of the portal vein and its tributaries from wedge hepatic venography. Selective hepatic arteriography may show reversal of flow in the portal vein with retrograde opacification of the latter.

Anatomic obstruction of vessels within the liver and arteriovenous and veno-venous shunts contribute to ischemia of the liver parenchyma.

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THE EFFECT OF BRADYKININ ON RENAL ARTERIOGRAPHY*

EXPERIMENTAL OBSERVATIONS

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BRADYKININ is a vasoactive nonapeptide present in an inactive form in plasma. The salivary glands, kidneys, pancreas and other tissues contain enzymes capable of activating bradykinin.[5] Synthetic bradykinin, indistinguishable from the naturally occurring substance, was first synthesized in 1960. Experimentally, it was found to have a remarkable vasodilating effect in both humans and animals.[5,12] Following direct administration of bradykinin into the renal artery of dogs, renal blood flow increased by a factor of two or more, while systemic pressure remained the same, suggesting marked arterial vasodilatation.[15,18] For this reason, it was thought that this agent might be useful as a pharmacodynamic adjunct to renal arteriography.

This is a preliminary report on the effect of bradykinin on renal arteriography. Observations on the use of this drug in conjunction with superior mesenteric and celiac arteriography have been reported by Boijsen and Redman,[3] and others.[18]

MATERIAL AND METHOD

A series of 53 experiments were carried out in 11 mongrel dogs, weighing between 13 and 20 kg., anesthetized with sodium pentobarbital, 30 mg./kg. Femoral artery cutdowns were performed. In 27 experiments, a single renal artery was catheterized using a 50 cm. red Kifa catheter with a 1 cm. precurved tip. In 7 experiments, the renal arteries were catheterized bilaterally. In 19, one renal artery was catheterized and a second tip-occluded injection catheter (125 cm. Rodriguez-Alvarez No. 7) was positioned above the origin of the renal arteries.

Bradykinin* was injected by hand into the renal artery, the amount varying from 0.015 to 0.5 μg./kg. (2–10 μg./dog) in a constant volume of 2 cc. of saline solution. Most experiments were carried out using between 0.1 and 0.25 μg./kg.; in 10 experiments a greater or smaller amount of bradykinin was used.

Renografin 60 was the contrast agent employed in amounts of either 0.15 or 0.4 cc./kg. for selective injections, 0.5 or 1 cc./kg. for bolus injections. In all but 6 experiments, the larger volumes of contrast material were used. Most of the selective injections were done by hand. Bolus injections were made using a Cordis injector, 40 cc. syringe, 300 pounds per square inch pressure. Some selective injections were also made with the Cordis injector, 150 pounds per square inch pressure.

Roentgenograms were obtained using a Franklin film changer, program 4/sec.×3 seconds, 1/sec.×8 seconds. The rate of injection of contrast medium could be estimated from the timed filming sequence and was approximately 6–8 cc./sec. for most selective injections, 16–20 cc./sec. for bolus injections.

In all experiments, controls were obtained using identical experimental conditions with the exception of the substitution of saline for bradykinin. In bilateral selective injections and bolus injections, the nonbradykinin injected kidney also served as a control.

* Generously supplied by Sandoz Pharmaceuticals, Hanover, New Jersey.

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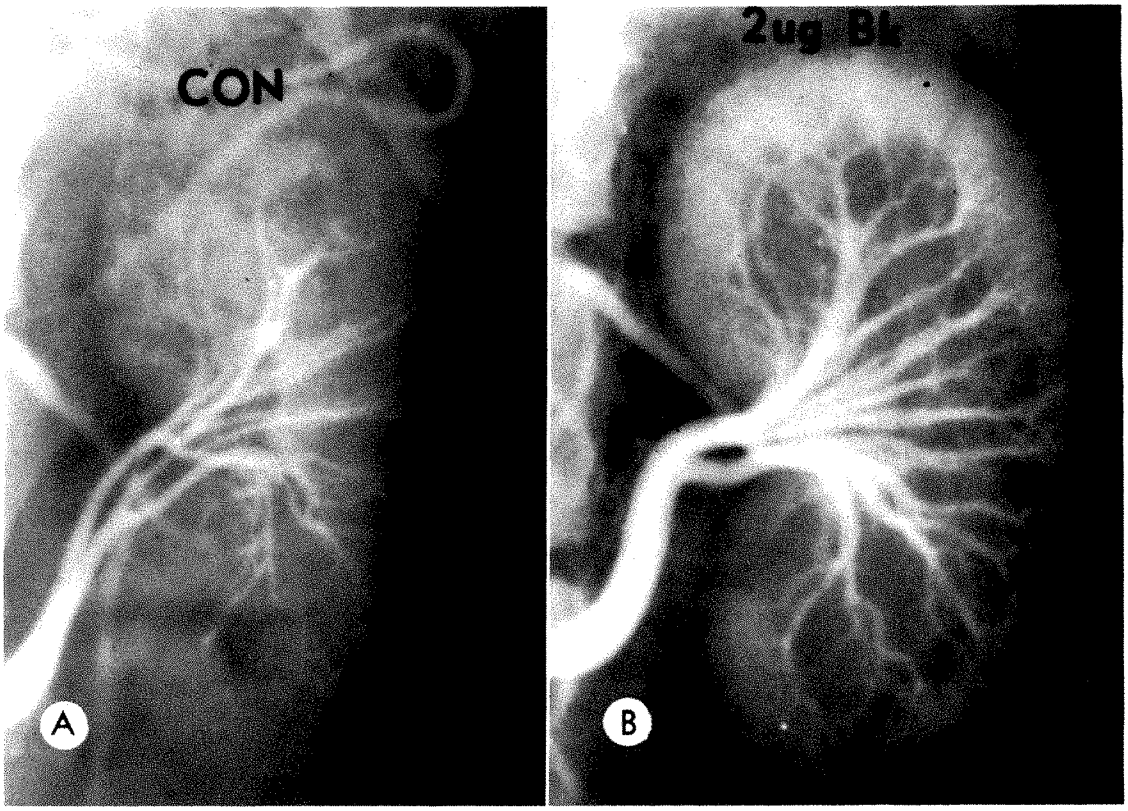

Fig. 1. (*A* and *B*) Note the marked increase in size of dorsal and ventral renal artery branches, interlobar and arcuate branches in *B* as compared to control in *A*. The interlobular branches are faintly visualized, whereas these were never visualized on control studies.

In some dogs, aortic or renal arterial pressure was recorded using a Sanborn 267B transducer and Sanborn recorder. In 2 dogs, micropaque was injected *in vivo* using selective renal catheters with 1 kidney receiving bradykinin prior to micropaque injection. The kidneys were removed, fixed in formalin and sectioned. Roentgenograms were obtained using a 1.5 mm. focal spot tube, focal spot-film distance of 40 inches, 300 ma., 26 kv., $1\frac{1}{2}$–3 second exposure (depending on thickness of section). Type M industrial film was used with hand processing.

RESULTS

Arteriograms following bradykinin injection revealed a number of constant differences in comparison with control arteriograms. There was marked increase in size of dorsal and ventral renal arterial branches and interlobar branches. The arcuate arteries and interlobular branches could be visualized, whereas in controls the latter were never visualized and the former were usually difficult to visualize (Fig. 1, *A* and *B*). The effect of bradykinin on the arcuate and interlobular branches can be better appreciated on photographic enlargements of sections of kidneys injected with micropaque *in vivo*, 1 kidney serving as a control, the other receiving bradykinin (Fig. 2, *A–D*). The initial cortical nephrogram, beginning one-half second after onset of injection and maximum $\frac{1}{4}$–$\frac{1}{2}$ second after completion of injection, was more intense following the injection of bradykinin (Fig. 3). Early renal vein visualization was always noted with bradykinin ($\frac{1}{4}$–$\frac{1}{2}$ second postinjection) and only occasionally seen in controls. The comparative density of the early visualized renal vein was much greater following the injection of bradykinin, the maximal renal den-

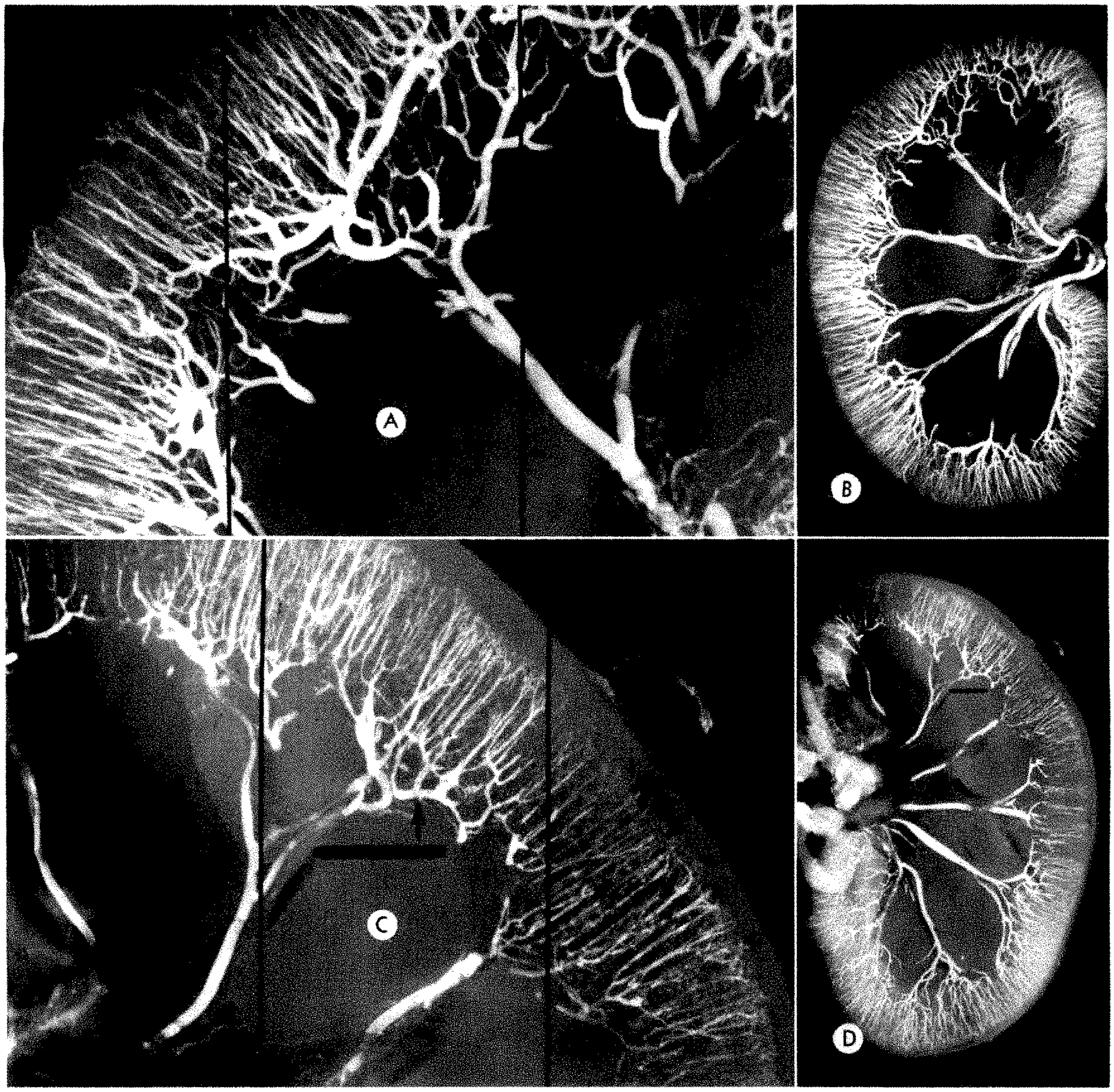

FIG. 2. (*A* and *C*) Photographic enlargements (×5.8) are demonstrated of the bradykinin injected and control kidneys, respectively. Note the marked increase in size of the arcuate (arrows) and interlobular branches of the bradykinin injected kidney in *A*. (*B* and *D*) *In vivo* injections of micropaque. The kidney in *B* received 2 μg. of bradykinin prior to simultaneous selective injections of micropaque.

sity occurring ½–1 second following completion of injection; in controls, maximum density occurred later, 3–5 seconds following completion of injection (Fig. 4). Aortic reflux, following selective injection of the contrast medium, was markedly diminished (Fig. 5, *A* and *B*).

These constant effects with bradykinin were maximal at a dose of 0.1 μg./kg. At higher doses of bradykinin, qualitatively similar but less marked changes were present. At the higher doses of bradykinin, aortic pressure dropped, whereas at the optimal dose range, pressure remained constant.[18] The intensity of the cortical nephrogram and renal vein density varied with the volume of contrast medium injected, and were more pronounced with the larger volumes of contrast material.

Some effects of bradykinin were variable. These included irregular opacification of the outer cortex (Fig. 6), seen to a greater degree and more frequently than in the controls. The medulla frequently appeared

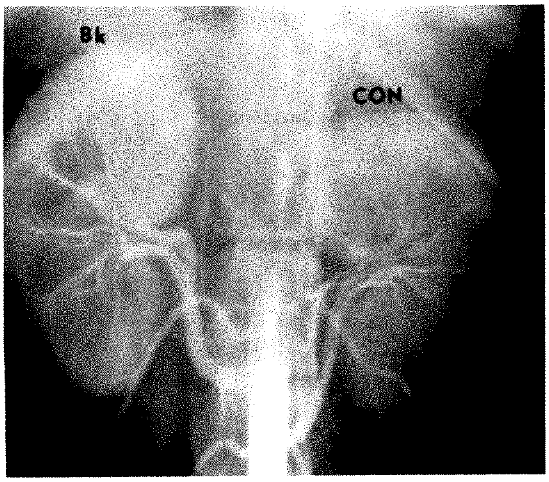

Fig. 3. Note increased intensity of cortical nephrogram on bradykinin injected side (1 second after onset of injection of contrast medium using bolus catheter).

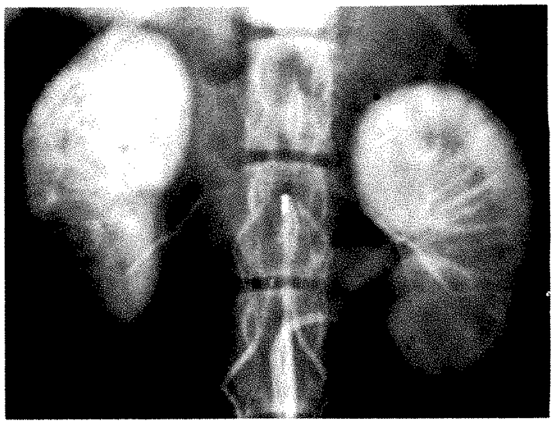

Fig. 4. Note intense early opacification of left renal vein (single arrow) 1 second following completion of contrast medium injection. Bradykinin (2 μg.) was injected into the left renal artery. The right renal vein (double arrow) of the control kidney is faintly opacified. There is decreased opacification of the medulla as compared to the control.

less well opacified following bradykinin, particularly during the time interval one-half second after onset of injection to 1 second after completion (Fig. 4; and 6). In some experiments, horizontal and vertical measurements of the kidney increased 5–7 per cent. This occurred in both control and bradykinin injected kidneys. The aorta and lumbar vessels appeared smaller following bradykinin injection (Fig. 7, *A* and *B*).

The primary nephrogram, occurring 2–6 seconds following completion of the contrast medium injection, was not significantly changed by bradykinin. It appeared that the density of the primary nephrogram decreased with greater rapidity following

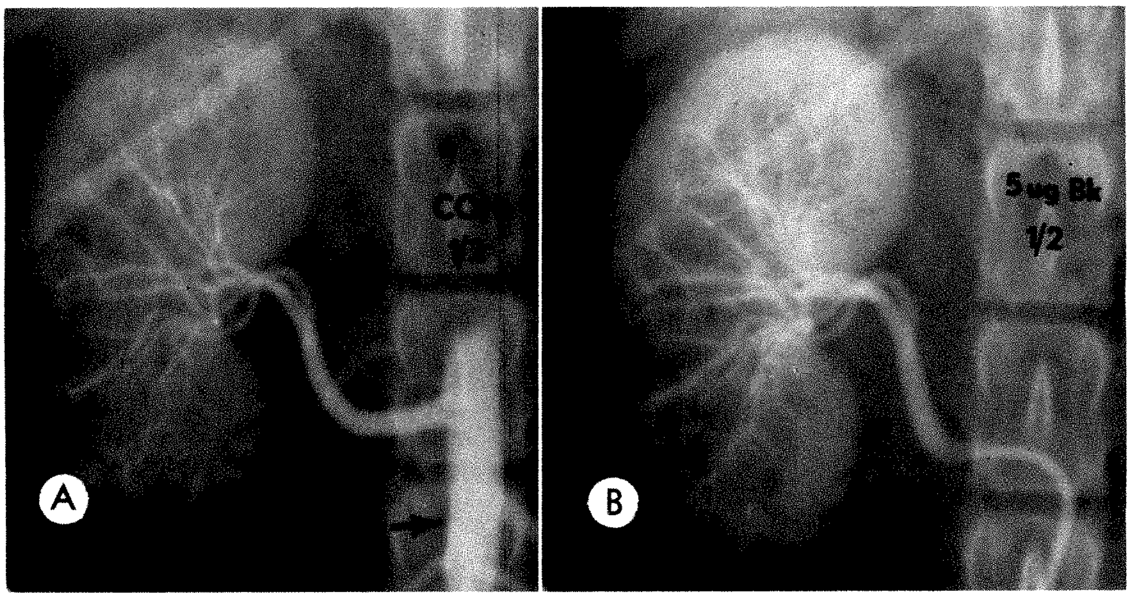

Fig. 5. There is marked reflux on the control side (*A*) one-half second after start of contrast medium injection. There is no reflux after bradykinin injection (*B*).

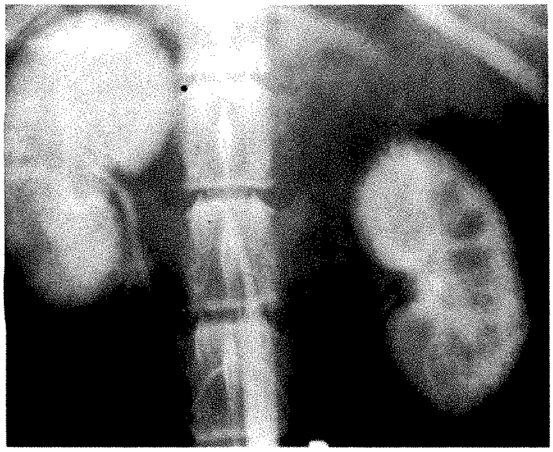

Fig. 6. Note the irregular opacification of the outer cortex of the left kidney (bradykinin side) in comparison with the homogeneous opacification of the outer cortex of the right kidney (control). This "frayed" appearance was frequently seen following bradykinin but was usually not as striking. Also note the apparent increased lucency of the medulla on the bradykinin injected side.

bradykinin injection; however, the filming program was not carried out long enough to adequately evaluate this.

DISCUSSION

The arterial dilatation is probably the result of a direct effect of bradykinin on arterial smooth muscle. The arterial dilatation decreases intrarenal vascular resistance. This decrease in resistance, in conjunction with constant intrarenal arterial pressure, accounts for the marked increase in renal blood flow noted when using bradykinin in a dose range of 0.1 μg./kg.[18] The increase in renal blood flow appears to account for the increased intensity of the cortical nephrogram. Part of the increased density of the cortical nephrogram may be illusory because of apparent decreased opacification of the medulla. The decreased vascular resistance and increased renal blood flow probably account for the decrease in reflux following selective injections.

The early intense opacification of the renal vein may be related to several factors. If the rate of contrast medium injection exceeds the rate of renal blood flow and proceeds long enough, contrast medium will fill capillaries and venules and will be excreted in the renal vein at a rate equal to cortical flow.[4] In many of the control injections, this phenomenon probably did occur, accounting for the early visualization of the renal vein in control experiments. This same explanation, in part, probably accounts for the early visualization of the renal vein following bradykinin injection. This, however, does not explain the increased intensity of the early renal vein opacification as compared to the controls. This finding can simply be a manifestation of increased renal blood flow; however, the possibility of shunting by either true arteriovenous communications or by alterations of regional blood flow must also be considered. Arteriolae rectae verae which arise from arcuate arteries or afferent arterioles in the corticomedullary region and connect directly with venules are one possible anatomic site for shunting.[1,14] This type of communication is present in small numbers in normal individuals and probably could not account for a significant degree of shunting.[14] The "Trueta" shunts increase blood flow to the corticomedullary region at the expense of the outer cortex and thus, in effect, allow alterations in regional blood flow.[17] Experimental evidence suggests the possibility of altered regional flow either by "Trueta" shunts or some other anatomic pathway, *e.g.*, increase of renal venous para-amino hippuric acid (PAH) occurring concomitant with a rise in renal blood flow following intra-arterial administration of acetylcholine. (Acetylcholine in many respects seems similar in its effect on renal blood flow to bradykinin.[7,9,10]) Whether shunting occurs, and the degree to which it contributes to the early intense renal venous opacification noted, cannot be proven from these experiments; however, this possibility should be considered.

Shunting, secondary to bradykinin, may account for the irregular opacification of the outer cortex we observed; however, various noxious stimuli including stimulation of the periarterial nerve plexus can also cause reduced flow to the outer cortex and

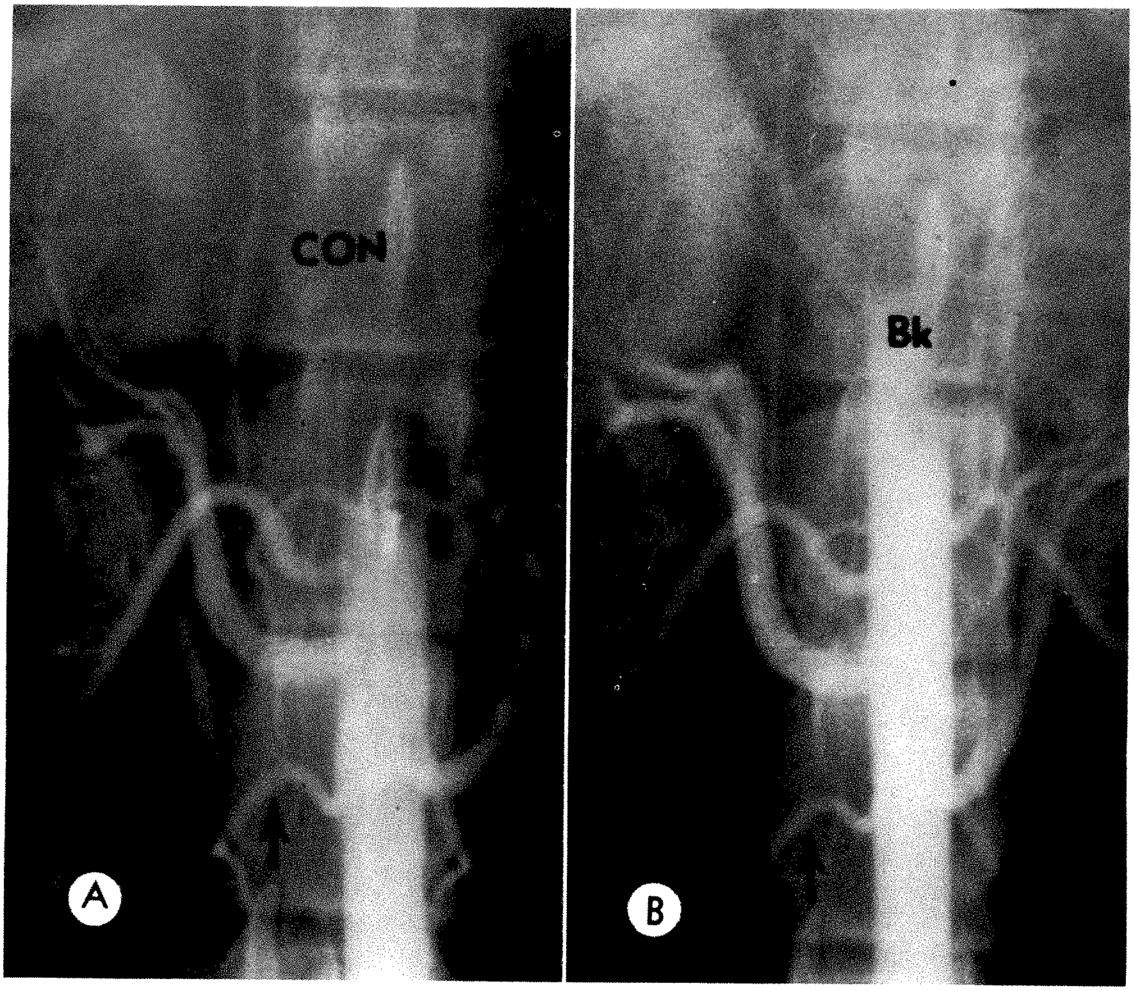

Fig. 7. (*A* and *B*) Arrows indicate comparable lumbar branches which are smaller following bradykinin injection into the right renal artery (note increased size of the dorsal and ventral arterial branches in *B*). The aortic width is also smaller on the bradykinin injected side.

cannot be excluded as a possible explanation for our results.[11] The apparent decreased opacification of the medulla may also be a reflection of regional alterations in renal blood flow.[10]

The observed decrease in size of the abdominal aorta and lumbar branches may be due to a homeostatic mechanism reducing regional blood flow to counterbalance the bradykinin induced increase in renal flow, thus maintaining a constant systemic pressure. The observed increase in renal size may reflect the effect of multiple injections of contrast medium rather than a bradykinin effect, since it involved both kidneys when both were injected with contrast material.[16]

The density of the primary nephrogram is determined by the volume of contrast medium in the peritubular capillaries.[4] The lack of change of the primary nephrogram, as observed in the period 2–6 seconds following completion of the contrast medium injection, probably indicates that the volume of contrast medium in the peritubular capillaries is not changed following bradykinin injection. It is possible that with bradykinin the initial volume of contrast medium was greater, but a rapid disappearance rate, related to increased renal blood flow, accounted for the absence of any definite difference in density as compared to controls.

The observation that bradykinin causes

distinct changes in the canine renal arteriogram suggests that the use of bradykinin may be of value as a pharmacodynamic adjunct to renal arteriography in humans. It may be of value in evaluating renal vascular changes in hypertensive patients causing qualitative or quantitative changes which may be significantly different from the normal. It may intensify the vascularity in relatively avascular renal tumors, such as renal pelvic carcinomas. Bradykinin infusion may even be of therapeutic value in patients with acute cortical necrosis or the rejection syndrome following renal transplantation. Currently, bradykinin is not available for use in human investigative work, and thus it may be worthwhile to consider the use of other vasodilators having similar effects on renal blood flow such as acetylcholine.[8]

SUMMARY AND CONCLUSIONS

An experimental technique has been described for evaluating the effect of a vasodilator, bradykinin, on renal arteriography in canines. Bradykinin causes marked arterial dilatation, increased density of the early cortical nephrogram, early intense opacification of the renal vein, and marked decrease in aortic reflux. The optimal dosage of bradykinin is 0.1 μg./kg. The effects produced by bradykinin are probably a manifestation of alterations in renal blood flow with increase in flow secondary to decreased vascular resistance accounting for most of the observed changes. It is possible that regional alterations in blood flow may, in part, account for the early intense renal venous opacification.

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ANGIODYSPLASIAS OF THE ABDOMINAL VISCERA ASSOCIATED WITH HEREDITARY HEMORRHAGIC TELANGIECTASIA*

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HEREDITARY hemorrhagic telangiectasia has long been defined as a familial disease characterized by the presence of telangiectasia of the skin and mucous membranes. Recurrent bleeding, most commonly epistaxis, has been the hallmark of this inherited vascular anomaly. Lesions of the lips, oral cavity, respiratory tract, urinary tract, liver, spleen, eye, brain, meninges, spinal cord and bone[8] attest to a multiplicity of system involvement as a facet of this disease. This great complexity does not appear to have received sufficient attention. We have therefore undertaken an intensive investigation of gastrointestinal bleeding and the visceral manifestations of the syndrome. Our study has been directed toward the pathologic vascular anatomy of the lesions of the abdominal viscera, since this material has not been previously detailed.

Angiography has demonstrated several heretofore unrecognized pathologic lesions and visceral-vascular shunts. Recognition of widespread anatomic vascular abnormalities has rapidly increased our knowledge of the disease and improved our understanding of the therapeutic problem that exists. The purpose of this interim report is to present the evidence that is being accumulated to support a concept that an angiodysplasia of the abdominal viscera is an integral part of hereditary hemorrhagic telangiectasia.

Determination of the specific lesions responsible for gastrointestinal hemorrhage in hereditary hemorrhagic telangiectasia has remained an enigma. Thirteen per cent of the patients have melena or hematemesis. There is a 6 per cent incidence of duodenal ulcer in the patient population with this disease and approximately half of the patients reveal lesions of the lips. It is interesting that the incidence of telangiectasia of the lips increases to 85 per cent in the gastrointestinal bleeders and the incidence of duodenal ulcer rises to 19 per cent.[22] With the exception of ulcer demonstration, routine roentgenographic examinations of the upper gastrointestinal tract, small bowel and colon have uniformly failed to show the lesions of this disease. There are, however, reports of positive findings seen at the time of gastroscopy and sigmoidoscopy.[2,9,10,13,14,18,19,24] Telangiectasia and phlebectasia of various abdominal organs and the intestine have also been noted during exploratory laparotomy and at autopsy.[4,6,13,16,21] Multiple aneurysms of the splenic artery have been reported in association with hereditary hemorrhagic telangiectasia.[20]

The application of visceral angiography to the study of gastrointestinal bleeding in these patients is recent. Multiple arteriovenous anastomoses in the liver[17] have been shown and a hepatic artery aneurysm combined with a portal vein fistula was demonstrated preoperatively.[11] In this latter instance, liver biopsy and postmortem examination revealed diffuse angiectasia without evidence of intrahepatic shunts or of cirrhosis. Hepatosplenomegaly in hereditary hemorrhagic telangiectasia has been thought to be coincidental or perhaps due to hepatic telangiectasia or posthepatic cirrhosis.[1,3,12]

The primary vascular lesion of heredi-

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tary hemorrhagic telangiectasia involves capillary and venous channels.[1,3,5,15,23] The vessel walls are thin and composed of a single layer of endothelial cells supported only by a fine layer of connective tissue. No elastic layer is present. Ectasia is a prominent feature producing tortuosity, coiling and conglomerate vascular masses which may be recognized as arteriovenous fistulae. The basic vascular abnormality is similar in all of the involved organs. Gross inspection of the abdominal viscera may reveal scattered sites of localized phlebectasia. Typical telangiectasia can be found on the surface of the liver and intestinal tract, but are more apparent upon inspection of the gastric and intestinal mucosa. The lesions are primarily submucosal but may extend into the muscularis externa. Occasionally varices protrude beneath the surface epithelium. Our case material to date seems to indicate that intrahepatic lesions are not confined to the portal venous system. The hepatic histopathology in 5 patients revealed portal fibrosis in all cases. In 4 of the 5 there was dilatation of the portal vein, bile duct ectasia and evidence of atrophy and regeneration of the liver. This appeared to be an ischemic type of atrophy. Three patients revealed dilated hepatic veins and angiomata were present in 2. Thrombosis is an integral part of hereditary hemorrhagic telangiectasia and is the probable explanation for pain in this disease. Pathologically, scattered thrombi and eccentric intimal venous thickenings are found. Two of the patients to be reported experienced episodes of epigastric pain as a prodrome to gastrointestinal bleeding.

REPORT OF CASES

Case I. *Pulmonary arteriovenous fistula and gastroduodenal artery-superior mesenteric vein fistula.* J. E., a 50 year old Negro female, gave a long history of recurrent epistaxis and gastrointestinal bleeding. The patient had been subjected to subtotal gastrectomy without relief of gastrointestinal bleeding. Episodes of epigastric pain and low back pain served as prodromata to the appearance of melena. Telangiectasia was present on the face, lips, buccal mucosa, tongue and skin. There was a bruit present over the midabdomen. Classic angiomata were seen at the time of gastroscopy; sigmoidoscopic examination was normal.

Roentgenographic findings. 1. Pulmonary angiogram: A pulmonary arteriovenous fistula 2 cm. in diameter was present at the right lung base. 2. Abdominal aortogram (Fig. 1): A saccular arteriovenous fistula 3 cm. in diameter shunted blood from the gastroduodenal artery directly into the superior mesenteric vein. There was dense opacification of the superior mesenteric and portal veins.

Case II. *Multiple pulmonary arteriovenous fistulae and intrahepatic arteriovenous shunts.* J. J., a 62 year old Caucasian male, presented with a long history of frequent epistaxis, recurrent gastrointestinal bleeding and anemia. There was no history of hematuria or hemoptysis. Telangiectasia was present on the lips, tongue and oral pharynx and spread diffusely over the skin. Multiple telangiectatic lesions were noted at gastroscopy; sigmoidoscopy was normal.

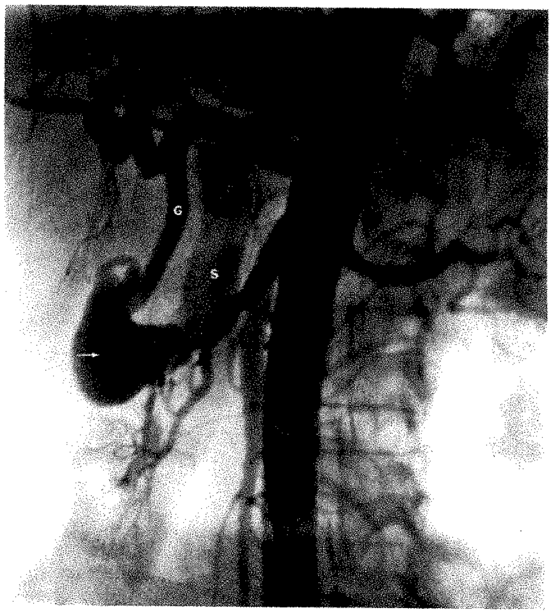

Fig. 1. Case 1. Abdominal aortogram in the right posterior oblique projection demonstrates the gastroduodenal artery and a superior mesenteric vein fistula. G = gastroduodenal artery; S = superior mesenteric vein; arrow = fistula.

Roentgenographic findings. 1. Pulmonary angiogram: Arteriovenous fistulae were present in the posterior basal segment of the left lower lobe and in the inferior segment of the lingula: one was 3 cm. in diameter, the other was 1 cm. in diameter. 2. Visceral angiograms (Fig. 2, *A* and *B*): The peripheral divisions of the intrahepatic arteries became indistinct and in place of discrete arterial channels a diffuse somewhat blotchy hepatic blush was noted. Peripheral hepatic venous branches were well opacified in segments of the liver. This finding is evidence of hepatic artery-hepatic venous shunt at the capillary level.

Fig. 2. Case II. Selective celiac angiograms show an intrahepatic vascular shunt of the hepatic artery to the hepatic veins. (*A*) Arterial phase. R = right hepatic artery; L = left hepatic artery; Arrow = left gastric artery branches. (*B*) H = arrows point to opacified branches of the hepatic vein; G = plexiform type of angioma in fundus of stomach. Note the small, malrotated right kidney.

Fig. 3. Case III. Celiac angiogram demonstrates multiple angiomata throughout the liver represented by small discrete areas of tissue staining (small arrows). Draining hepatic veins are present (arrowheads).

Case III. *Angiomatosis of the liver and multiple arteriovenous malformations of the ascending colon.* B. L., a 63 year old Caucasian male, gave a long history of recurrent epistaxis. There was no history of hemoptysis, hematemesis, melena or hematuria. There was an increasing number of episodes of congestive heart failure. Classic angiomata were seen in the stomach at the time of gastroscopy; sigmoidoscopic examination was normal. There was telangiectasia on the face, lips, buccal mucosa and skin.

Roentgenographic findings. 1. Pulmonary angiogram: The examination was normal. 2. Visceral angiograms (Fig. 3; and 4, *A*, *B* and *C*): The peripheral intrahepatic branches gave rise to a myriad of small, stellate areas of dense hepatic staining and there was opacification of several peripheral hepatic venous branches. Two separate arteriovenous malformations were present adjacent to the wall of the proximal portion of the ascending colon and ileocecal valve. Dense opacification of the draining veins was present with early filling of the ileocolic vein.

Case IV. *Intrahepatic arteriovenous shunts and multiple splenic artery aneurysms.* S. R., a 61 year old Caucasian female, gave a history of massive recurrent epistaxis and several major gastrointestinal hemorrhages. Telangiectasia was present on the lips, oral and nasal mucosa and scattered over the skin. The patient gave no history of hemoptysis or hematuria. She noted that epigastric pain tended to precede the episodes of gastrointestinal bleeding.

Roentgenographic findings. 1. Pulmonary an-

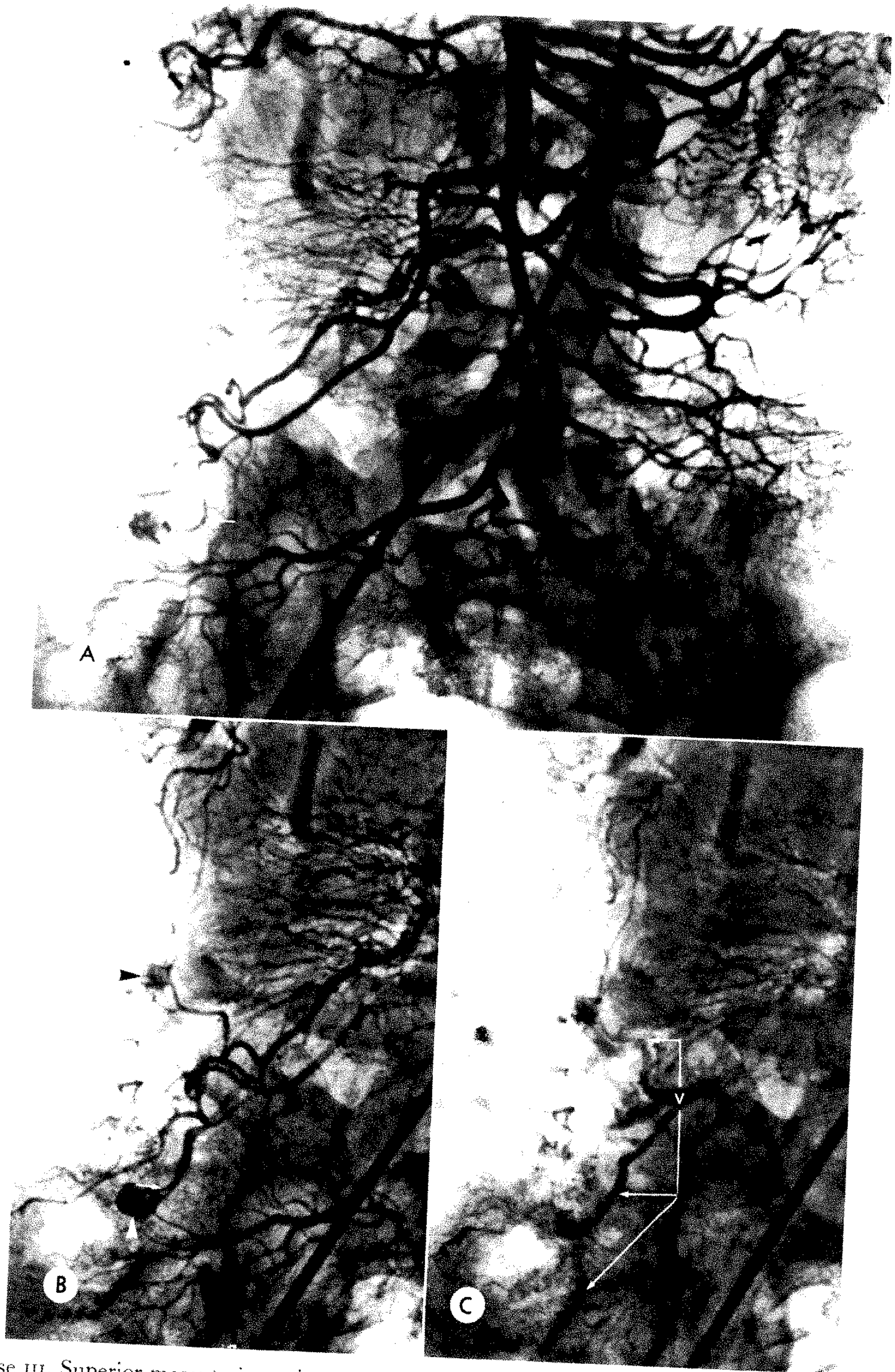

FIG. 4. Case III. Superior mesenteric angiograms. (*A*) Early arterial phase. A small colonic arterial branch leads to 1 site of vascular malformation (arrow). (*B*) Late arterial phase. Two vascular malformations are now apparent (large arrowheads). The colonic arterial branch supplying the inferior lesion is still opacified (arrow) and early filling of a draining vein can be seen (small arrowheads). (*C*) Capillary phase. Dense opacification of the veins draining the vascular malformations is evident (arrows). V = ileocolic vein.

giogram: The examination was normal. 2. Visceral angiograms (Fig. 5; and 6, *A* and *B*). The right lobe of the liver was examined separately by selective catheterization of a replaced right hepatic artery which took origin from the superior mesenteric artery. The primary intrahepatic branches were normally distinct but the smaller arterial branches appeared as irregular streaks and small blotchy areas of contrast. Moderate opacification of a few peripheral branches of the hepatic veins was present. The primary branches of the left hepatic artery gave rise to a conglomerate mass of "pathologic" vessels which resulted in a dense hepatogram of the left lobe of the liver. There was an early, intense opacification of the left hepatic veins. Three distinct aneurysms of the splenic artery were present. There were no identifiable abnormalities of the mesenteric vessels. Selective renal angiography demonstrated the presence of a 6 cm. benign renal cyst in the lower pole of the left kidney.

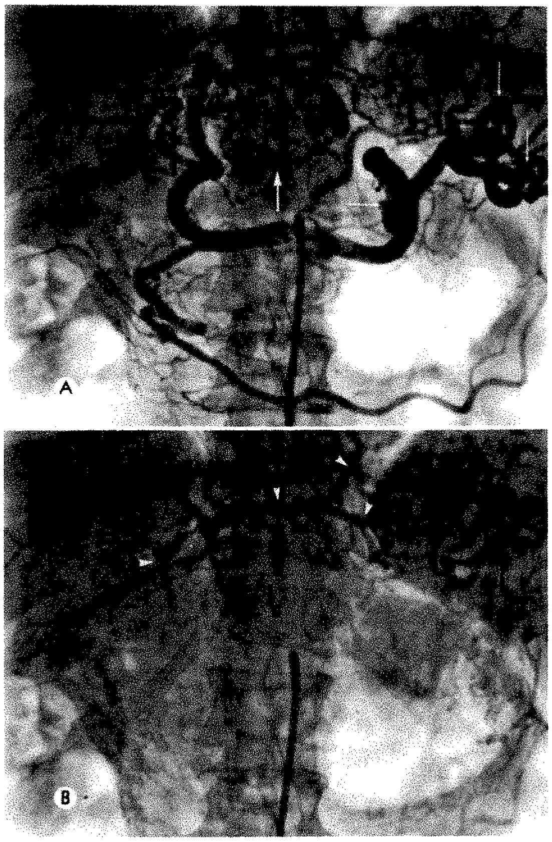

Fig. 6. Case iv. Celiac angiograms. (*A*) Arterial phase. The vascular bed of the left lobe of the liver shows gross malformation of the arterial branches (large arrow). Three separate aneurysms of the splenic artery are present (small arrows). (*B*) Capillary phase. There is dense opacification of the left hepatic vein branches (arrowheads).

ANGIOGRAPHIC FINDINGS

Four cases have been selected from a group of patients with hereditary hemorrhagic telangiectasia and gastrointestinal bleeding who were subjected to a thorough angiographic study of the abdominal viscera. A variety of arterial-capillary-venous abnormalities were demonstrated: arteriovenous fistulae and malformations, multiple angiomata, discrete aneurysms and arterial-capillary angiectasia with venous shunting. Hemodynamic shunt at the capillary level was recognized through an early dense opacification of the regional draining veins. It should be stressed that hepatic veins are not normally visualized during the course of hepatic angiography.

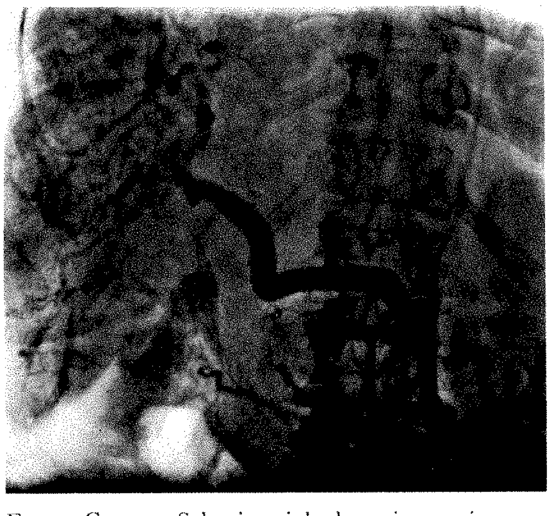

Fig. 5. Case iv. Selective right hepatic arteriogram. Gross malformation of the intrahepatic arterial branches is present.

The initial phase of this investigation of gastrointestinal hemorrhage in patients with hereditary hemorrhagic telangiectasia utilizing the diagnostic procedure of visceral angiography has produced a more complete anatomic definition of widespread vascular abnormalities, providing a broader insight into the possible mechanism for gastrointestinal bleeding in these patients.

A variety of dysplastic vascular lesions and vascular shunts have been found. Angiography is partially resolving the difficult task of locating the lesions of hereditary hemorrhagic telangiectasia which have proven to be quite elusive at the time of surgery, even in the instances of massive intestinal bleeding. Certainly this new knowledge extends our ability to understand the therapeutic problem presented by these patients and provides an explanation for failure of surgical treatment, since extirpation of only a segment of the disordered vascular anatomy is possible. It is important, however, to realize that the angiographic lesions that are demonstrated do not necessarily represent the site of origin of the gastrointestinal bleeding in a given patient. The frequent findings of angiectasia and duct ectasia in the liver have raised the question of hematobilia as a cause of melena. While hematuria has not been part of the clinical picture of any of our patients to date, we are somewhat intrigued by the presence of a benign renal cyst in 1 patient and small, malrotated but vascularly intact kidneys in 2 other patients. The detailed clinico-angiographic correlation of our complete investigation of hereditary hemorrhagic telangiectasia will be presented as a separate report.[7]

SUMMARY

Angiographic investigation of gastrointestinal bleeding in patients with hereditary hemorrhagic telangiectasia has demonstrated a somewhat indiscriminate distribution of a variety of arterial, capillary and venous abnormalities often showing hemodynamic shunts.

It is suggested that hereditary hemorrhagic telangiectasia be defined as an inherited, diffuse, pleomorphic angiodysplasia.

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THERMOGRAPHY AND HERNIATED LUMBAR DISKS*

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PRELIMINARY studies indicate that thermography is a useful procedure for demonstrating the presence and location of herniated lumbar disks and may be either supplementary or complementary to myelography.

Thermography is the pictorial representation of a range of temperature variations of a scanned area. The technique from a medical aspect was originated in the mid 1950s by R. N. Lawson. He recognized the association of an area of elevated skin temperature with breast cancer. Thermography of breast cancer was further investigated by Lloyd-Williams *et al.*,[7] Wallace *et al.*,[8] and Gershon-Cohen *et al.*[4] Wood[9] and others have utilized thermography in the evaluation of cerebral insufficiency, and Cosh[3] pioneered its use in arthritis. Albert *et al.*[1] reported its use in orthopedic problems and included a scan of a patient with a herniated disk. Goldberg *et al.*[5] reported abnormal heat patterns in 4 of 21 persons with herniated disks.

While it is apparent that the signal sensed is a skin temperature alteration, the results of the investigators cited above indicate that the signal may be the reflection of a deep underlying process. The mechanism for transfer of heat energy from a deep structure to the skin has been incompletely investigated. The description of Cooper *et al.*,[2] of a vascular connection of the heat of an active muscle to the skin may apply.

TECHNIQUE OF THERMOGRAPHY

The technique of thermography is simple from both technical and clinical aspects. The patient is examined in the sitting or prone position. The back is exposed and allowed to equilibrate with the 70° F. room temperature for 6–8 minutes. The scans are then made at 3 sensitivity settings, each scan taking 30 seconds. A Pyroscan (Lloyd-Williams) is used. It is modified to give improved detector cell performance and increased signal to noise ratio and selection of polarity for pictorial presentation. The 3×41/2 inch recording is made on standard newspaper facsimile paper which requires no processing.

METHOD OF STUDY

Ninety-three patients with symptoms and signs suggesting herniated disks received thermograms followed immediately by myelography. Twenty-nine were operated and herniated disks removed. The thermographic findings were compared to the myelographic findings. Also, control thermograms were compared to the 29 herniated disk thermograms.

RESULTS

Control-back thermograms in healthy individuals reveal variable hot spots but there are 4 areas which reveal fairly constant features. There is a warm area in the center of the back which extends from the scalp hair line to the level of the 5th lumbar vertebra and corresponds to the vertebral spinous processes. It varies in width and may present as a fusiform widening in the upper lumbar area but narrows again in the lower lumbar area (Fig. 1, *A* and *B*). Below this is a clear area and then another central-warm area corresponding to the intergluteal cleft. Immediately above and lateral to the level of the intergluteal cleft are symmetric warm areas that extend 2 or 3 inches caudally and corre-

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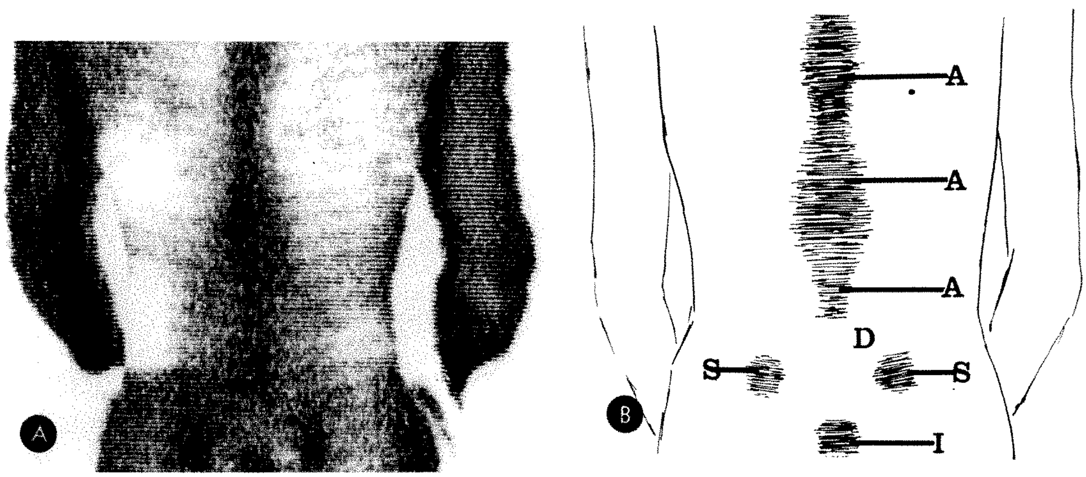


Fig. 1. (*A*) Control thermogram. (*B*) Diagram of control thermogram. The central hot spot is fusiform at the lumbar area and extends from the upper thoracic spine to a level above the sacroiliacs (A). Bilateral hot spots are noted overlying the sacroiliacs (S). The intergluteal fold is noted below the sacroiliac shadows (I). Most herniated disks will show a hot spot in the region between the central hot spot and the sacroiliac (D).

spond to the sacroiliac joints (Fig. 1*B*). None of these warm areas need be present or they may be of varying widths and extent. A relatively *cold* area is invariably present between the end of the central-warm area of the spinous processes, the sacroiliac warm area, and the intergluteal area; and it is in this region that the warm spots due to herniated disks are found.

Abnormal thermograms were present in 23 of the 29 patients with herniated disks and appeared usually as a warm area extending obliquely caudal from the normal central hot spot, either unilaterally or bilaterally and localized to the level of the herniated disk (Fig. 2, *A–C*; 3, *A–C*; 4, *A–C*; and 5, *A–C*). Occasionally, the abnormal-warm areas were multiple and round and occurred beside and below the normal-central-warm area (Fig. 2, *A–C*).

Of the 29 patients operated, the myelogram revealed a herniated disk at the proper level in 23. There were 3 false positive (disks described at different levels than found at surgery) and 3 false negative studies (Table I).

Thermography indicated herniated disks at the proper level in 23 studies. There were 5 false negative scans and 1 false positive (Table I).

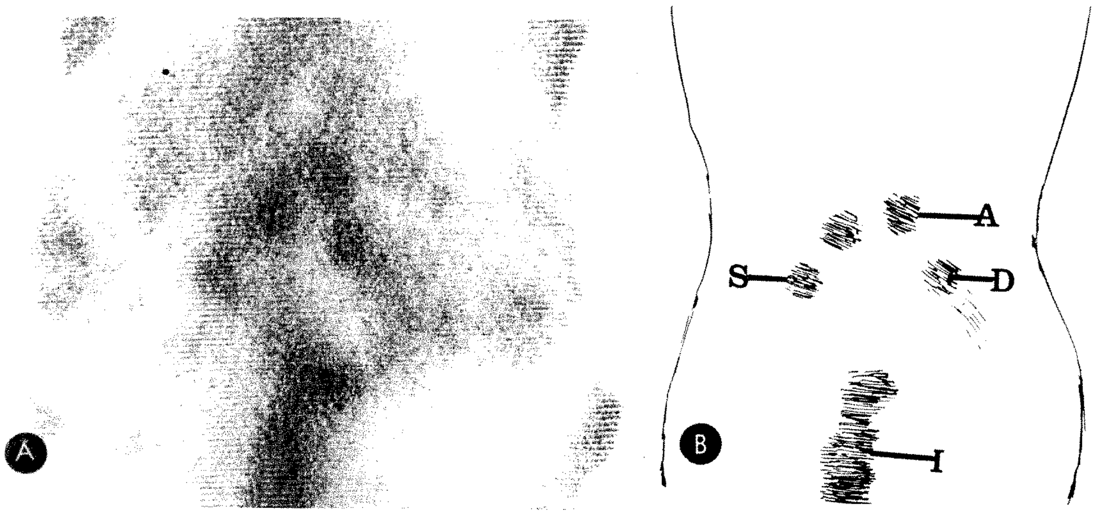
In 19 patients the myelogram and thermogram revealed similar results and in 10 the results were dissimilar (Table II). In 18 the disk was found at the indicated level. In the 1 patient with a negative myelogram and thermogram, a herniated disk was found (Table III).

In 10 patients myelography and thermography revealed different findings. In 5 instances the myelogram was correct; in 5 others the thermogram was accurate (Table IV).

DISCUSSION

The majority of patients with herniated lumbar disks present symptoms and signs so characteristic that the diagnosis is assured and the disk accurately localized. The use of myelography in these patients is to confirm the diagnosis. A minority of patients with herniated disk will present atypical signs and symptoms and myelography is necessary for accurate diagnosis. However, myelography presents certain disadvantages:[1] it may be a painful procedure with painful side effects;[3] there is a potential danger of infection and arachnoiditis;[4] and in certain instances the herniated disk is not demonstrated because of failure of encroachment on the subarachnoid space or proximal nerve roots.

Thermography is a simple procedure



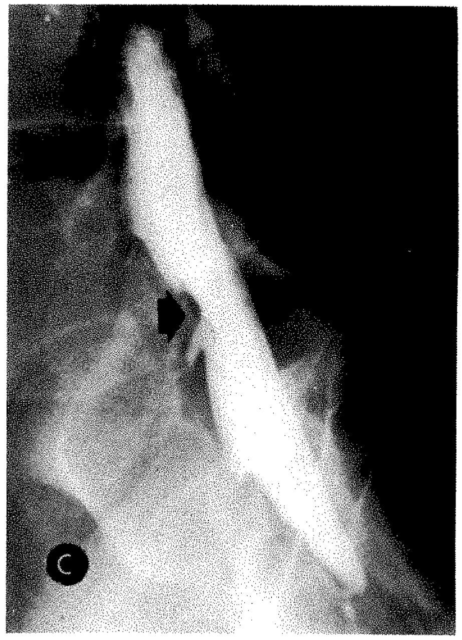


Fig. 2. (*A*) Thermogram of patient with herniated disk. (*B*) Diagram of *A*. There is no central hot spot over the spinous processes but the end of the spinous processes may be seen at A. The sacroiliac hot spot shows on the left side (S). The intergluteal fold is also demonstrated (I). A hot spot due to a herniated disk is noted (D). This is between the hot spot of the normal sacroiliac and the end of the normal central warm spot. (*C*) Myelogram on same patient indicating a herniated disk (arrow).

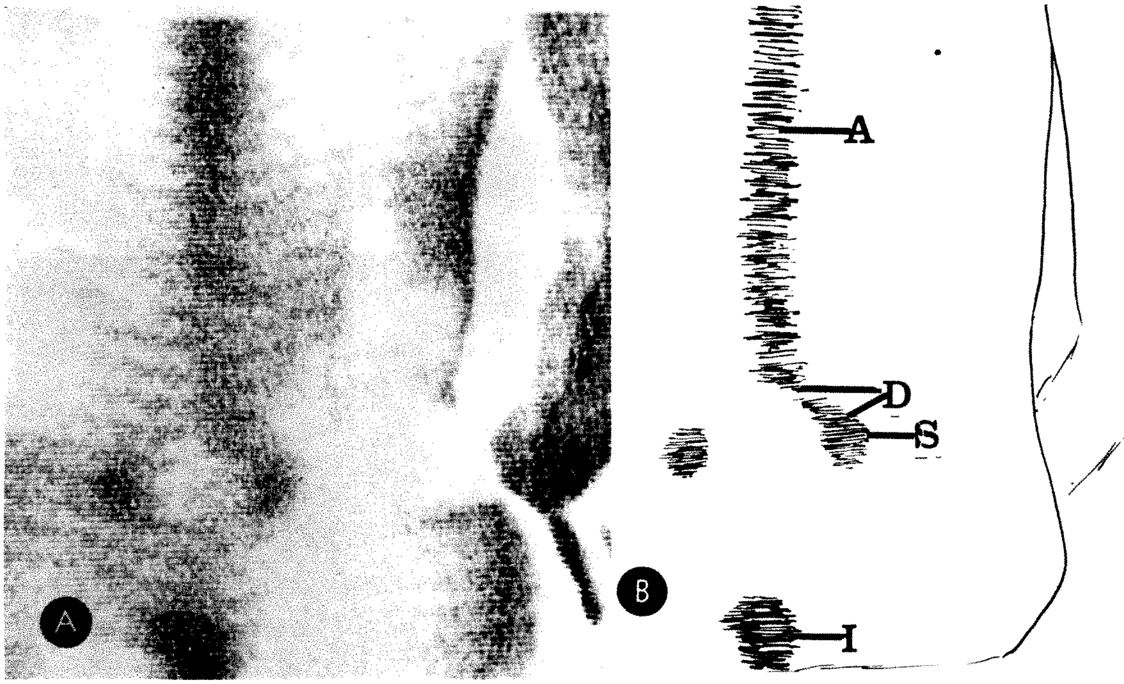
which may compensate for the myelographic disadvantages. The preliminary studies indicate that thermography may either be supplementary or complementary to myelography.

It is noteworthy that in 26 patients, myelography and thermography were both positive in 23 cases. Goldberg *et al.*[5] reported only 4 active thermograms in 21 proven cases. Improved thermographic techniques account for the better results in our study.

Thermography presented fewer false positive but more false negative studies. In the 10 patients with different results, thermography was correct in 5 and myelography accurate in 5. This suggests that thermography compares favorably with myelography for the diagnosis of herniated disk.

CONCLUSION

Thermography is a simple procedure unassociated with morbidity. In the presence



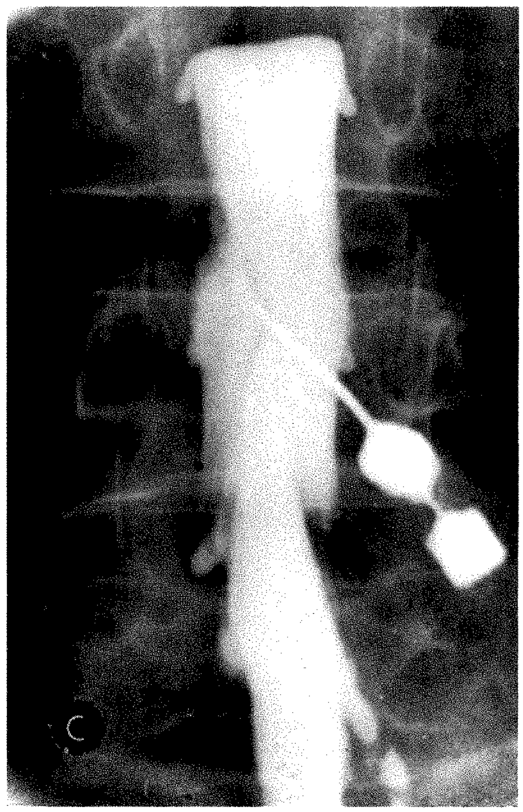
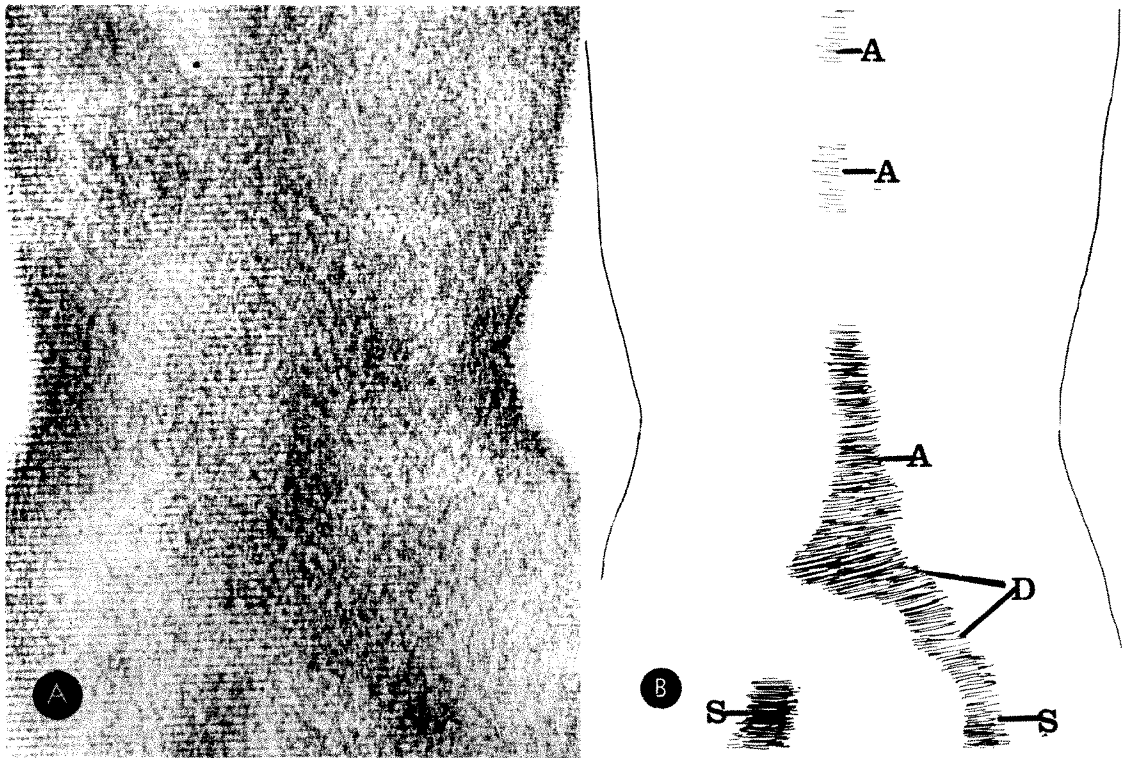


Fig. 3. Herniated disk on the right. (*A*) Thermogram. (*B*) Diagram of *A*. The normal central warm spot is present (A), both sacroiliac warm spots are present (S), as well as the intergluteal fold (I). The abnormal warm area subtended between the central warm spot of the spinous processes and the sacroiliac (D) reflects a herniated disk. (*C*) Myelogram revealing the herniated disk (arrow).



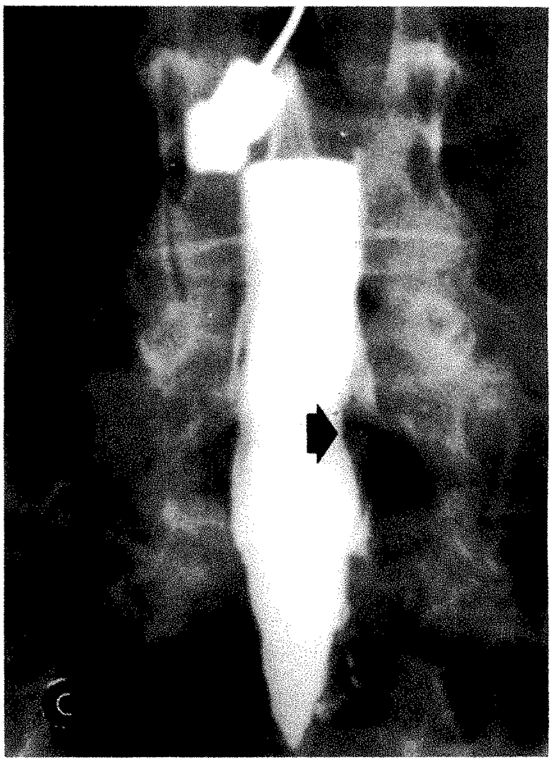


Fig. 4. Herniated disk. (*A*) Thermogram of herniated disk. (*B*) Diagram of *A*. The central hot spot over the spinous processes is irregular (A). Both sacroiliac hot spots are present (S). The hot spot between the central hot spot and the sacroiliac hot spot is due to the herniated disk (D). (*C*) Myelogram revealing herniated disk (arrow).

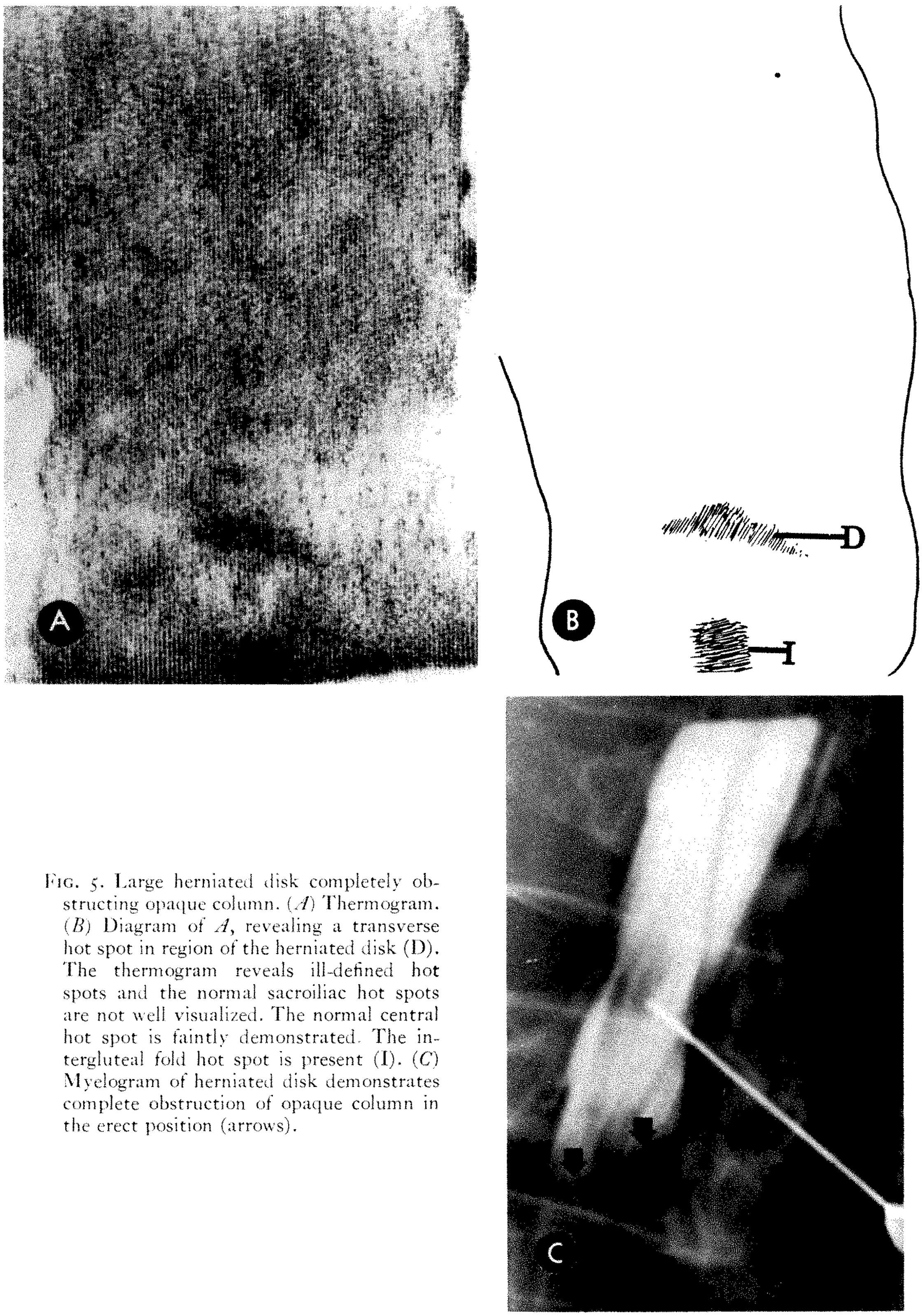


Fig. 5. Large herniated disk completely obstructing opaque column. (*A*) Thermogram. (*B*) Diagram of *A*, revealing a transverse hot spot in region of the herniated disk (D). The thermogram reveals ill-defined hot spots and the normal sacroiliac hot spots are not well visualized. The normal central hot spot is faintly demonstrated. The intergluteal fold hot spot is present (I). (*C*) Myelogram of herniated disk demonstrates complete obstruction of opaque column in the erect position (arrows).

Table I

29 PATIENTS OPERATED FOR HERNIATED DISKS

	Study Accurate	False Positive	False Negative
Myelography	23	3	3
Thermography	23	1	5

Table II

COMBINED RESULTS IN 29 PATIENTS

	Similar	Dissimilar
Studies	19	10

Table III

SIMILAR MYELOGRAPHY AND THERMOGRAPHY FINDINGS IN 19 PATIENTS

Correct	Incorrect	Total
18	1	19

of herniated disk, a characteristic abnormal skin temperature elevation may occur over the site of disease and may be recorded thermographically. The thermographic and myelographic results were similar and combined results indicated the site and diagnosis of 28 of 29 herniated disks. This preliminary study indicates that thermography is an excellent complementary procedure. In some instances, thermography may supplement myelography.

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Table IV

DISSIMILAR MYELOGRAPHY AND THERMOGRAPHY FINDINGS IN 10 PATIENTS

Myelogram Correct	Thermogram Correct	False-Positive Myelogram	False-Negative Myelogram	False-Positive Thermogram	False-Negative Thermogram
5	5	3	3	1	5

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THE USE OF LOGICAL FLOW CHARTS AS AN AID IN TEACHING ROENTGEN DIAGNOSIS*

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IN AN analysis published in 1962,‡ it was argued that diagnostic errors derived not from technical imperfections in the roentgenogram, but rather from the erratic and often inappropriate response of the film reader to information recorded in the film. On the assumption that the response of the film reader might best be influenced through training, it was suggested that the development of improved teaching materials offered the most hopeful approach to more accurate roentgen diagnosis. Accordingly, in 1963, the development of a programmed course in roentgen diagnosis was undertaken to test the practicality of this suggestion.

As a first step, educational objectives were prepared which in accord with the principles of Mager[2] sought to define the specific activity of which the student was to be capable at the completion of the course. In brief, these objectives specified that the student should be able to conduct a logical analysis of a roentgen examination—detecting critical recorded shadows; discriminating normal from abnormal shadows; discriminating among various classes of abnormal shadows; and accurately identifying abnormal shadows, individually or in combination, with specific diagnostic possibilities appropriate to the particular type of roentgen study.

The programming consultant* proposed then that our teaching materials must provide the student with step-by-step directions concerning what to look for and how to proceed on the basis of the information extracted at each step of the film analysis. Simply to enumerate and illustrate the findings characteristic of various pathologic entities would not, he argued, prepare the student for the desired sort of terminal behavior. As a schema for the organization of the programmed frames, he proposed that for each roentgen examination to be presented, a logical, step-by-step system of analysis be developed and expressed in terms of a flow chart or decision tree analogous to those employed in computer programming. The development of such flow charts proved surprisingly difficult but correspondingly rewarding. Although they were initially intended only as guides to the preparation of programmed frames, their greater flexibility has led us more recently to abandon the programming effort and to center our attention on the use of the flow chart itself as a teaching device.

STRUCTURE OF THE FLOW CHART

In brief, the flow chart consists of a hierarchy or sequential system of progressively more specific questions leading ultimately to the most specific diagnostic output justified by the evidence at hand.

The characteristics of the flow chart are demonstrated in Figures 1–5. These flow charts represent the analysis of the roentgen examination of the colon by barium enema. This analysis has been divided into 5 broad concepts, and each of the flow charts illustrated represents the analysis with respect to one of these concepts.

The concepts chosen are: (1) completeness of *filling*; (2) *position* of segments; (3) *caliber* of lumen; (4) regularity of *margins*;

‡ John Blyth, Ph.D., Argyle Publishing Corp., New York, New York.

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This project was supported by a Community Cancer Demonstration Grant from the United States Public Health Service.
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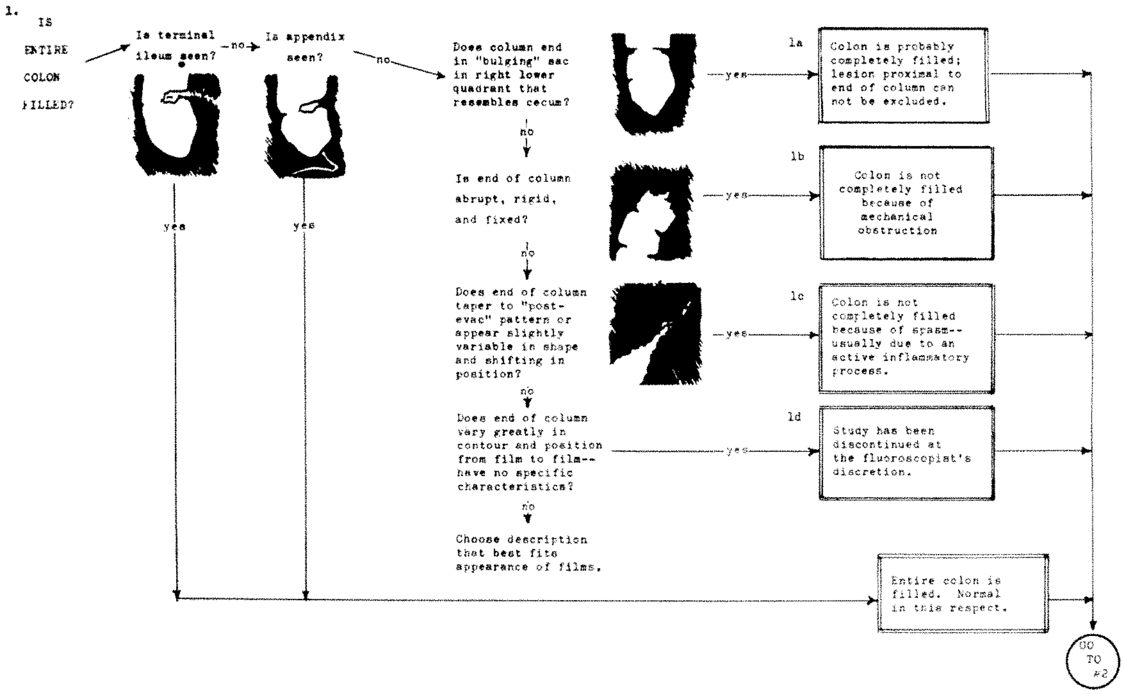

Fig. 1. Analysis of the roentgen examination of the colon. Flow chart for Concept 1.—Completeness of filling.

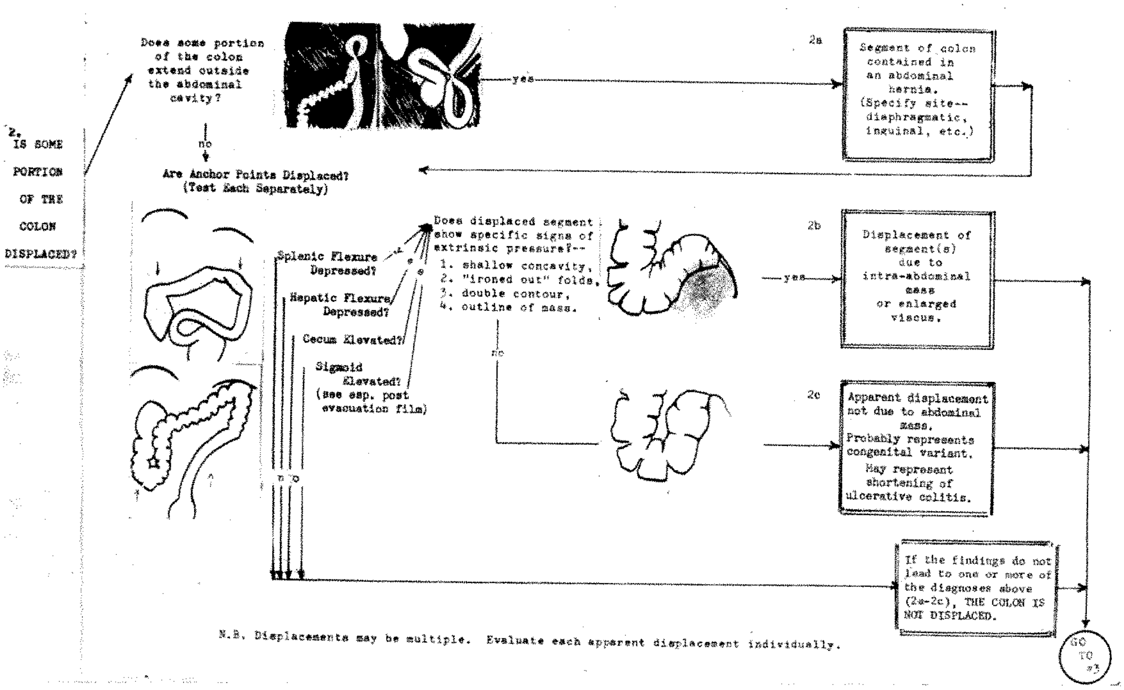

Fig. 2. Analysis of the roentgen examination of the colon. Flow chart for Concept 2.—Position of segments.

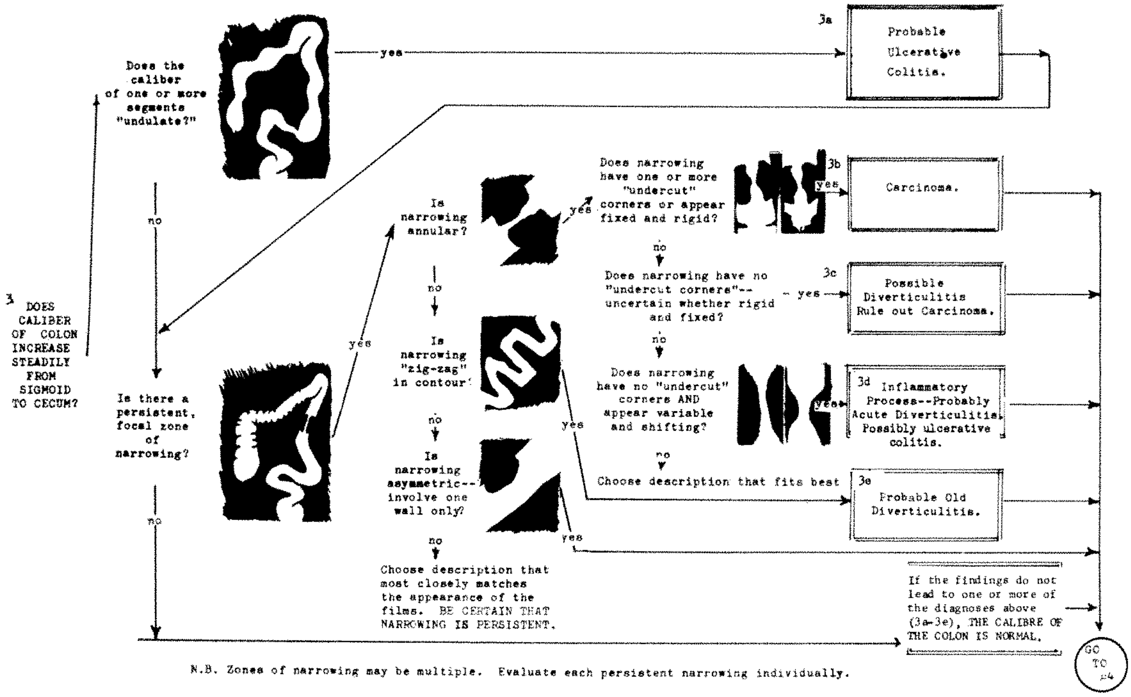

Fig. 3. Analysis of the roentgen examination of the colon. Flow chart for Concept 3.—Caliber of lumen.

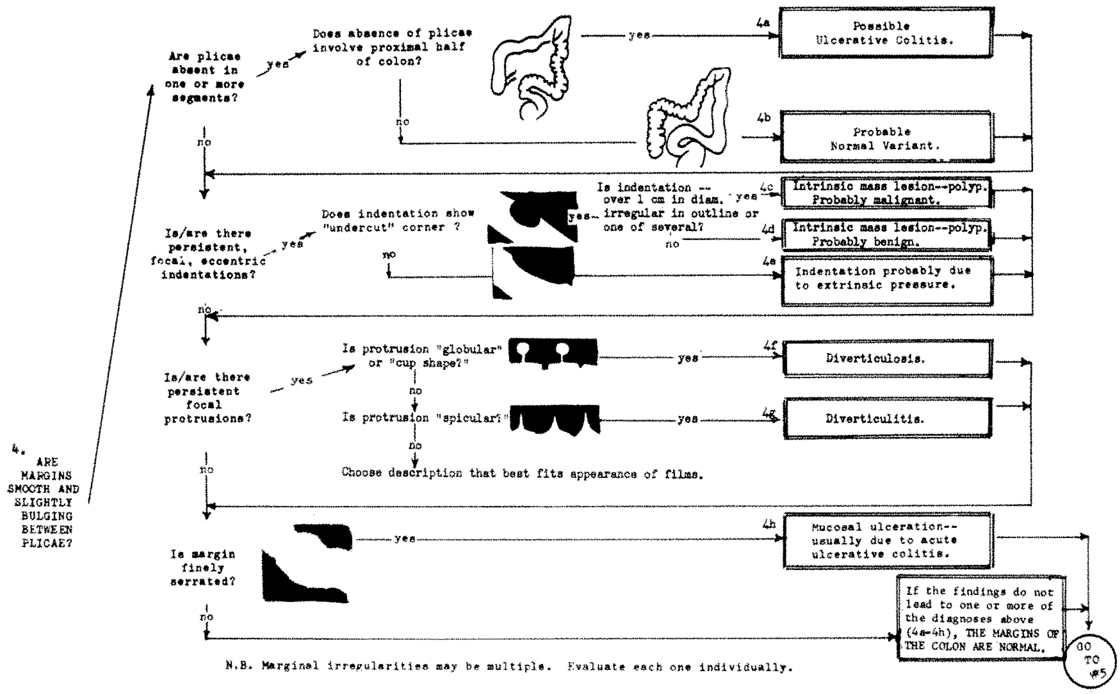

Fig. 4. Analysis of the roentgen examination of the colon. Flow chart for Concept 4.—Regularity of margins.

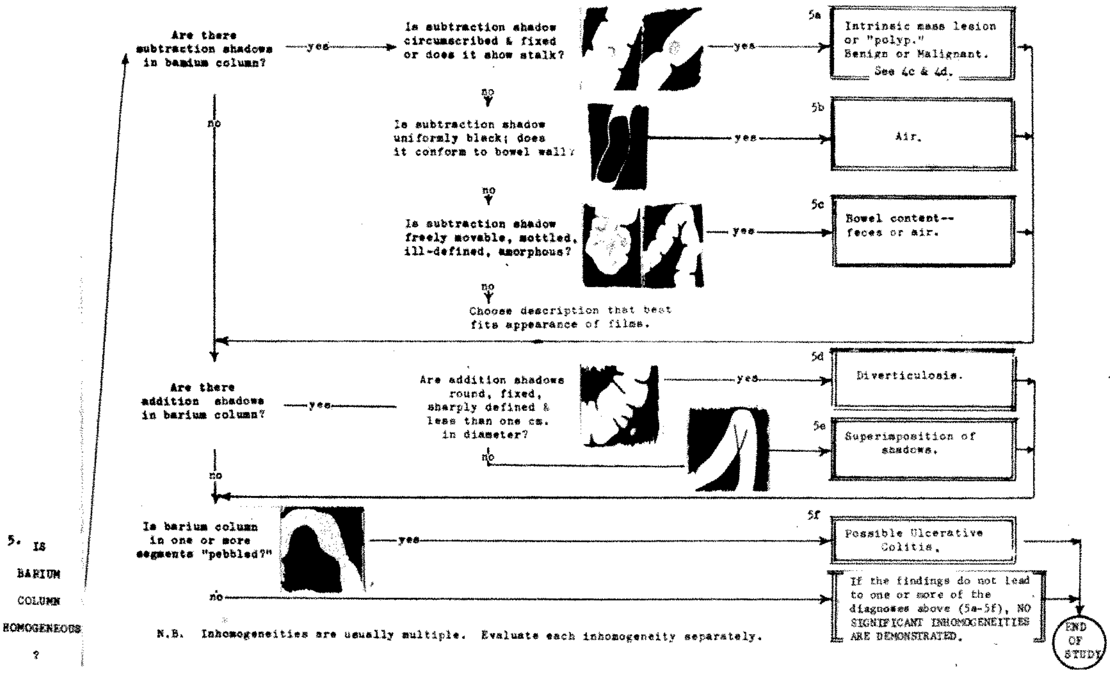

Fig. 5. Analysis of the roentgen examination of the colon. Flow chart for Concept 5.—Homogeneity of barium column.

and (5) *homogeneity* of barium column. These are, in a sense, equivalent to the more familiar parameters of "size," "shape," "number," etc. They appear to be a more useful mnemonic device with respect to studies of the gastrointestinal organs, however, because they provide more specific reminders of the abnormalities to be sought.

The following characteristics of the flow chart should be noted:

1. Every question requires a "yes" or "no" answer. The student is forced to make decisions based on his perception of the roentgenographic shadows—an important step in his training.

2. Each question answered—each decision made—determines the next step to be taken in the analysis. The student's course toward a diagnosis is unambiguously defined at every point.

3. The structure of the flow chart takes account of the fact that the characteristics of a particular shadow may not, in the student's judgment, match any of the possibilities presented to him by forcing him to choose the best match available. (Alternatively, he might be provided with a nonspecific output. For example, in Figure 1, an additional output, "Incomplete filling of uncertain significance," might be added as the conclusion to be drawn from a "no" response to the last question in the flow chart.)

4. Where multiple diagnostic outputs relating to a single concept may coexist, the student, having reached one output, is directed to return and consider the next series of questions to ensure that no diagnostic possibilities are overlooked (Fig. 2; 3; 4; and 5).

5. Sketches are included as mnemonic devices and to amplify word descriptions. Illustrations of some sort appear to be essential to the successful application of the flow chart. Such pictorial material might better, in the future, take the form of photographs, lantern slides, or cathode-ray tube displays.

6. The wording of the diagnostic outputs can be chosen to indicate the relative probability of various diagnostic possibilities,

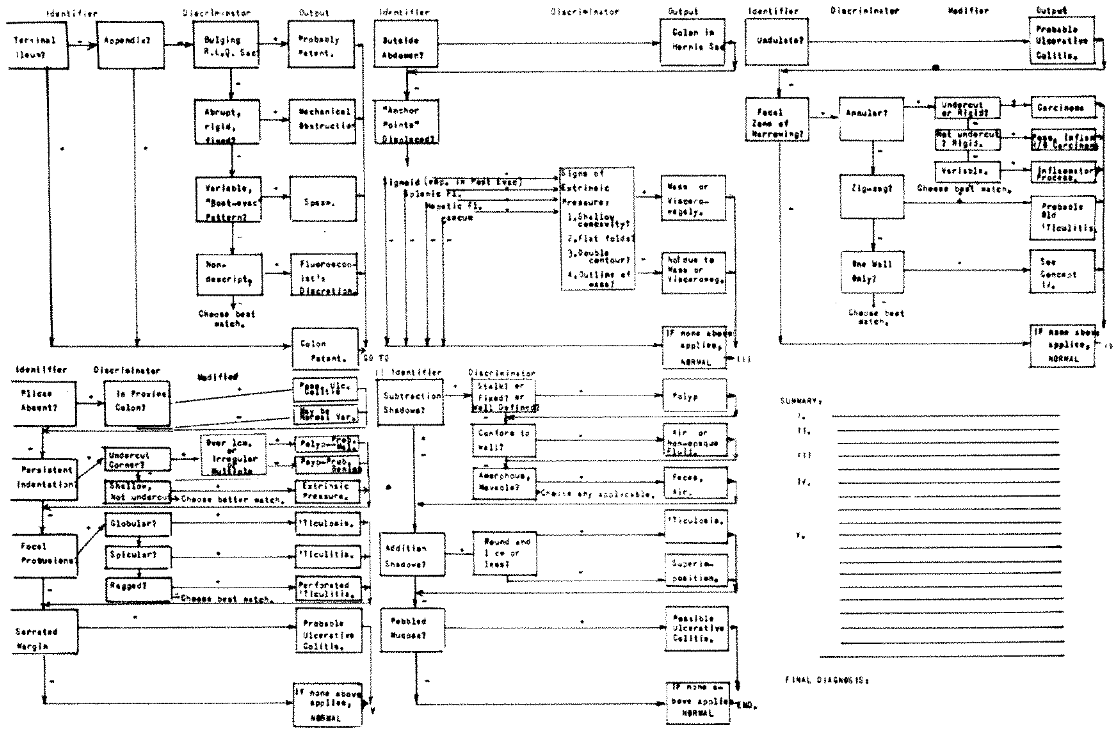

Fig. 6. Analysis of the roentgen examination of the colon. Student worksheet.

e.g., outputs 3b, c, and d in Figure 3. The introduction of probability judgments is another important aspect of student training.

7. Specific notations direct the student's attention to particular roentgenograms in a complex study and guide his identification of abnormalities that may be manifest differently in different segments of the colon (Fig. 2).

8. A final summary sheet (Fig. 6) is provided to permit the student to review the various diagnostic outputs he has reached and to integrate them into the most succinct and rational final diagnosis possible.

APPLICATIONS

Various applications of flow charts to the teaching of roentgen diagnosis are under study. Self-instructional programmed texts based on flow chart analyses of the barium enema study and cholecystographic examination have been completed, and the flow chart would appear to have potential value in the development of other types of self-instructional materials. Its most successful application to date has been in the conventional classroom situation, however.

In class work with medical students at Pennsylvania Hospital, representative examples of a particular roentgen examination are analyzed by an instructor in terms of appropriate flow charts. Students follow the analyses on copies of the flow charts with which they have been provided. Subsequently, in a workshop, each student is required to analyze additional examples of the examination under consideration and to trace his analysis on a worksheet—an abbreviated set of flow charts (Fig. 6). This written record is then reviewed with him, a process that is not only instructive to the student, but is helpful to the instructor in defining difficult visual discriminations and in detecting and resolving ambiguities in the wording of questions and outputs.

DISCUSSION

Finally, it is appropriate to consider some of the apparent advantages and dis-

advantages to the use of flow charts in teaching roentgen diagnosis.

First, in their favor, at least at a theoretic level, is the fact that the flow chart offers a direct approach to teaching the student to perform precisely the task that will be required of him. The flow chart presents a logical approach to film reading which is more generally applicable and philosophically more appealing than what Felson has referred to as the "Aunt Minnie" approach to roentgen diagnosis.

Second, the flow chart makes clear to the student the fact that abnormal shadows are of varying degrees of specificity and that diagnostic outputs of necessity involve probability judgments. The flow chart, thereby, gives the student some insight into the limitations of the method and heightens his understanding of the meaning of a carefully framed roentgen interpretation.

Third, in a different vein, the flow chart serves to guide the student's search strategy, and may help to control one of the major sources of reader error in this way. Since it appears that an effective search does not follow a geometric pattern, but rather is a reasonable seeking after successive clues, guided by partial information,[3,4] the flow chart may prove to be a much more effective guide to the development of effective search than such time honored admonitions as, "Look at the four corners of the film." Further, strict adherence to the flow chart would preclude premature discontinuance of search which appears to be one of the most significant sources of reader error.

Fourth, the hierarchal system of questioning which characterizes the flow chart provides clues or expectations with respect to subsequent findings. According to Hebb,[1] such expectancy may play a critical role in the perception of visual stimuli—a rather formal statement of the familiar adage, "You see what you expect to see." The expectancy provided by the flow chart then, may actually increase the likelihood of the student's perceiving critical shadows and may thus help to control another of the major causes of reader error.

At a more practical level, students are enthusiastic and express great satisfaction in the use of flow charts. Some of this may be a reflection of the novelty of the system, but to some extent it would appear that the flow chart does impart to the student a sense of "know how," a realization that there is nothing mystical in roentgen interpretation, a feeling that he, too, can "play the game." These attitudes, though difficult to quantify, may be tremendously important in recruiting students to this area of specialization.

On the other hand, it must be admitted that the flow chart greatly oversimplifies the processes of roentgen interpretation. In the example presented here, several relatively uncommon diagnostic possibilities are not represented at all and many supposedly useful diagnostic signs have been eliminated from consideration. It should be noted, however, that the flow chart can be amplified to include additional criteria and diagnostic outputs. The flow charts illustrated have been deliberately simplified to permit the student to visualize them, to learn them, and to "carry them with him." Similarly, questions concerning physical findings, laboratory data, and medical history might be added where pertinent. These, too, have been deleted in an effort to avoid the appearance of overwhelming complexity.

Further, it might be argued that the colon flow charts make no reference to pathologic processes occurring elsewhere in the abdomen. The solution to this defect, of course, lies in the development of additional flow charts dealing with the interpretation of other intra-abdominal shadows.

Another serious objection to the system lies in the fact that it remains an artificial system. No accomplished radiologist consciously approaches the analysis of a study in such a rigid, methodical, step-by-step fashion. There is some evidence, however, that the instantaneous recognition of complex visual stimuli is built upon the integration of numerous simpler percepts,[1] and perhaps the flow chart system will prove useful both in introducing new perceptual

material and in fostering this sort of integration.

Again, it should be noted that the flow charts presented here are based largely on introspection and are subject to all the errors of introspective analysis. Careful clinical validation is still in progress. Further, it is recognized that an individual's analysis of a roentgen study is probably a highly personal pattern of behavior, and that flow charts proposed by one radiologist may not satisfy another. The flow charts illustrated here, therefore, are presented only as tentative examples of a new teaching medium.

The preparation of flow charts is extremely time consuming and our experience is limited to studies of gastrointestinal organs. The system, however, is theoretically applicable to all roentgen examinations, and the conclusion that it is more productive to teach the student *how to analyze* a roentgenogram than to describe for him the findings typical of various disease states seems inescapable.

SUMMARY

Diagnostic flow charts analogous to those employed in computer programming but representing the processes of roentgen interpretation are proposed as an aid to teaching roentgen diagnosis. The structure of the flow chart—a hierarchy of successively more specific questions leading to specific diagnostic outputs—is illustrated, and the rationale of its use, both to guide search and to facilitate the analysis of observed abnormalities, is discussed. Its potential application to self-instructional teaching materials is noted, and early experience with its use in classroom teaching is described.

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THE EFFECT OF INCREASED OXYGEN TENSIONS .UPON ANIMAL TUMOR GROWTH*

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WITH the rapidly developing therapeutic use of increased oxygen tensions, attention is being focused on many basic, unanswered questions regarding the physiologic and biochemical effects of such increased oxygen tensions upon living tissue. Because of its application in combination with radiation therapy, either breathing 100 per cent oxygen or under hyperbaric conditions, the influence of high oxygen tensions on tumor cell growth is receiving particular attention.

Recently, 2 hybaroxic radiation centers[12,16] have reported a seeming increase in metastases following radiation therapy under hyperbaric conditions for advanced neoplasms. Whether exposure to hyperbaric oxygen (HPO) influenced metastatic growth in these cases is unknown.

The exact role of increased oxygen tensions in the spread and growth of metastatic tumors has yet to be explored in depth. Bean *et al.*[3] have shown that 6 atmospheres absolute (ATA) oxygen inhibits the growth of Erhlich ascites tumor cells *in vitro.* Similar *in vitro* results were obtained by others[2,8] using different tumor cells. The *in vivo* results have been reported variously as no inhibition of tumor growth[4,5,11,14,15] or as a decrease in metastases.[13] The time-pressure relationships have varied from 0.6–6.0 ATA oxygen for single exposures of 2–83 hours or multiple exposures on a daily or even weekly basis. In the majority of these studies, especially prior to 1964, the pressures employed were greater than those which could be used therapeutically.

The present study is designed to investigate the effects of oxygen, at time-pressure relationships within the human therapeutic range, on the growth and distribution of an established, rapidly metastasizing tumor.

MATERIAL AND METHODS

Animals. Rats (CFN albino, male, 160–180 gm.) were selected as the host animal because at the pressures employed in this study, they are relatively resistant to the pulmonary and central nervous system manifestations of oxygen toxicity. Animals were housed 4 to a metal cage and fed Wayne Lab Blocks and water *ad libitum.*

Tumor. A Walker carcinosarcoma R256, obtained from the tumor strain maintained in the Department of Pathology at Jefferson Medical College, was followed through 5 serial passages in our CFN rats. Constant growth characteristics and metastatic spread were noted in each generation. Sections of viable tumor (1–2 mm.) excised from the sacrificed donors were immediately transplanted into the right axilla via a 13 gauge trochar without anesthesia.

Chamber. An animal hyperbaric chamber was obtained on loan from Dr. J. P. Concannon of the Allegheny General Hospital. This cylindrical vessel measures 2 feet in diameter and 4 feet in length with a volume of 12.6 cubic feet. It comfortably holds 30 rats in 2 large wire cages. Two observation portals of 7.5 inches and 5.5 inches are located on the top and side of the tank. Baralyme granules were placed inside the chamber to absorb CO_2. The chamber was flushed at 25 liters/min. for 3 minutes with oxygen, then the pressure was raised to

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30 pounds per square inch gauge (p.s.i.g.) over 7–10 minutes. This was maintained for 60 minutes with flushing every 15 minutes at 25 liters/min. for 2 minutes to help prevent CO_2 accumulation and to maintain a constant temperature of 24–25°C. Continuous decompression was carried out over 7–10 minutes.

Experimental Design. Exposure of the rats to the various gaseous environments was instituted on the tenth day following tumor transplant. The animals were divided into 4 groups of 15 animals each. The exposure regimen consisted of a 1 hour daily exposure, on 5 consecutive days per week, to the following oxygen tensions: 1 atmosphere absolute (ATA) air control (152 mm. Hg), 3 ATA air (456 mm. Hg), 1 ATA oxygen (760 mm. Hg), and 3 ATA oxygen (2,280 mm. Hg).

All tumor-bearing animals in the first experimental series were sacrificed and autopsied after 8 oxygen exposures on the twentieth day after transplant. In the second series, the animals continued the above regimen until death; the last animal died on the thirty-third day after transplant. Autopsies were performed as soon as possible after death and the following information recorded for both series: weight of animal, weight of tumor and metastatic nodules, dimensions of tumors and nodules (volumes were calculated by the formula $4/3\ r_1r_2r_3$), weights and size of the lungs, spleen, liver, kidneys, and adrenal glands with sections of these organs taken for histologic study. In both series, special note was made of the distribution of lymph node metastases; to be counted, a nodule had to attain a minimum size of 0.5 cm. In one series, the longest diameter of the primary tumor was also measured daily until adjacent metastatic nodules made measurement difficult.

RESULTS

Preliminary studies showed that the CFN rat was resistant to the pulmonary and central nervous system manifestations of oxygen toxicity when exposed daily for 1 hour at 3 ATA oxygen, 5 days per week, for 3 weeks (the longest exposure that any tumor bearing animal experienced was 3 weeks). No convulsions were noted, they appeared comfortable in the chamber, sleeping through most of the 60 minutes, gained weight and no microscopic evidence of lung damage was found.

The typical pattern of growth of the Walker carcinosarcoma was the development of a 1.5 cm. axillary tumor mass in 1 week. This mass quadrupled in size over the next 10 days followed by palpable adjacent nodules in the axilla plus central necrosis of the primary tumor. The metastatic spread then involved, in chronologic order; the lungs, opposite axilla, adrenal glands, liver, mediastinum, cervical lymph nodes, inguinal lymph nodes, and finally the abdominal lymph nodes. Death from metastases occurred in approximately 4 weeks. The microscopic appearance of organ metastases was in the form of tumor cell nests, sometimes intravascular in nature. Also noted was an interstitial pneumonia associated with pulmonary metastases; this was not seen previously in either oxygen exposed or unexposed non-tumor bearing animals.

The first experimental series was terminated after 8 chamber sessions, the point when early metastases to adjacent axillary lymph nodes had just started. The data in Table 1 indicate no significant difference in the parameters measured in the experimental or control groups at this time. Microscopic examination of the adrenal glands (an early site of metastases) confirms the lack of an oxygen effect with small numbers of tumor cells noted equally in all groups.

Figure 1 shows the growth rate of the tumor as measured externally from the tenth to the seventeenth day after which time adjacent metastatic nodules prevented further accurate measurement. There were no marked external evidences of early differences in growth rate.

In the second series of experiments, the rats were exposed to oxygen from the

Table I

RESULTS OF 8 DAILY 1 HOUR HYPERBARIC OXYGEN (HPO) EXPOSURES UPON ESTABLISHED WALKER CARCINOSARCOMA R256

	Air Control*	Air 3 ATA*	Oxygen 1 ATA*	Oxygen 3 ATA*
Primary tumor weight (gm.)	33.2 ± 13.0	34.8 ± 12.6	34.3 ± 6.2	34.3 ± 6.2
Primary tumor volume (cm.³)	25.8 ± 12.1	26.8 ± 10.3	26.3 ± 5.3	25.8 ± 5.3
Lung weight (gm.)	02.1 ± 0.6	2.1 ± 0.6	1.8 ± 0.2	2.1 ± 0.9
Spleen weight (gm.)	2.5 ± 0.22	2.3 ± 0.6	2.1 ± 0.5	2.3 ± 0.5
Adrenal size (cm.)	0.5 ± 0.09	0.5 ± 0.05	0.5 ± 0.07	0.5 ± 0.09
Per cent of animals with axillary metastases	50	57	55	54

Note: Rats were exposed to HPO on Days 10, 11, 12, 13, 14, 17, 18, and 19 after transplant and sacrificed on Day 20. ATA = atmosphere absolute.
* Mean value ± S.D.

tenth day after transplant until death. The mortality among the experimental and control groups was similar (Fig. 2). The rats expiring between the eighteenth and thirty-third days after transplant were chosen for further analysis. (Further breakdown between the twenty-fourth and thirty-third day gave the same statistical results.)

The volume of the primary tumor in the second series showed a growth inhibiting effect of the increased oxygen tensions as reflected in the calculated mean tumor volumes (cubic cm.) of 50.7 ± 29.7, 37.9 ± 26.6, 20.6 ± 14.0, and 25.0 ± 10.0 for 1 ATA air, 3 ATA air, 1 ATA oxygen and 3 ATA oxygen, respectively. While the difference between 1 ATA air and 3 ATA air is not highly statistically significant, one notes a tendency towards a decrease in volume with the increased oxygen tension. Both 1

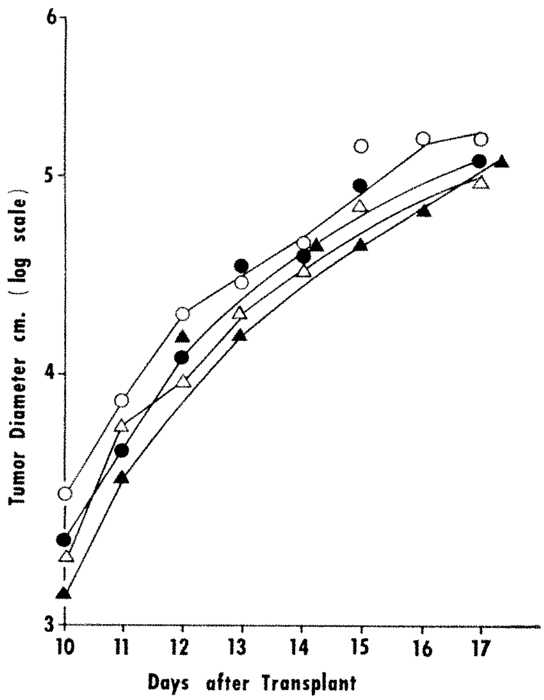

Fig. 1. Growth rate of Walker carcinosarcoma R256. Tumor was measured daily from Day 10 to 17 after transplant. ○ = control; ● = 3 ATA air; △ = 1 ATA oxygen; ▲ = 3 ATA oxygen.

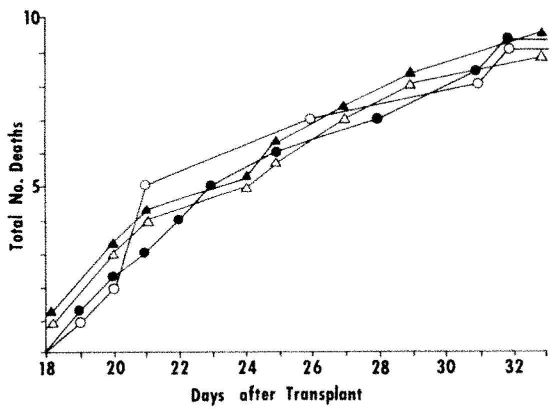

Fig. 2. Death rate of tumor bearing rats. HPO started on Day 10 after transplant of Walker carcinosarcoma R256. ○ = control; ● = 3 ATA air; △ = 1 ATA oxygen; ▲ = 3 ATA oxygen.

and 3 ATA oxygen as compared to the 1 ATA air control are significant at a $P_{(t)} < 0.05$.

Significant differences were also observed in the metastases. The mean number of metastatic nodules per animal was 2.55, 2.55, 2.00 and 1.89, respectively, for the 1 ATA air, 3 ATA air, 1 ATA oxygen, and 3 ATA oxygen. A composite distribution of these nodules depicted in Figure 3 reveals the marked inhibition of distant metastatic spread by increasing oxygen tensions; this is especially evident below the level of the diaphragm. This halt in the normal chronologic pattern of tumor spread is supported by the histologic findings in our preliminary studies. Estimates of the number of tumor foci within the lungs, adrenals, and livers of these animals were half as great for the 3 ATA oxygen group as compared to the 1 ATA air group.

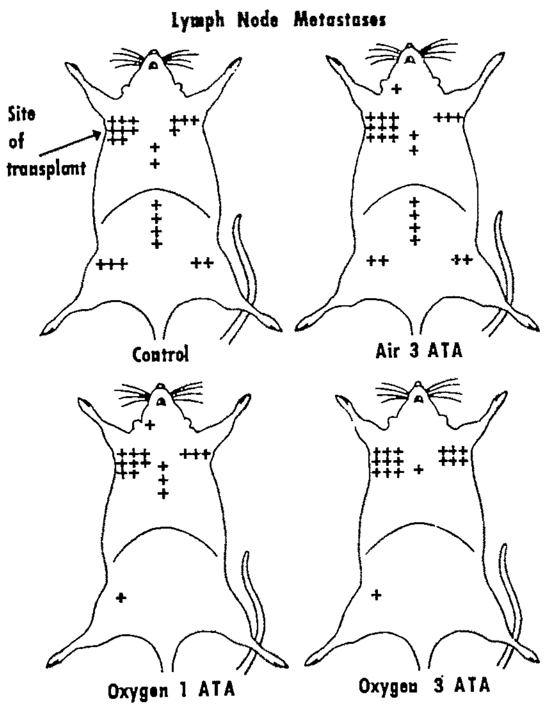

FIG. 3. Schematic representation of lymph node metastases. Walker carcinosarcoma R256 was transplanted into the right axilla of the rat and exposure continued from Day 10 after transplant to death. + = 1 metastasis.

DISCUSSION

The primary purpose of this investigation was to contribute to the understanding of the effects of increasing oxygen tensions upon the *in vivo* growth and distribution of a rapidly growing and metastasizing tumor. The combination of time and pressure is a prime determinant as to the nature of the results obtained; sufficient exposures at adequate oxygen tensions will cause the inhibition of tumor cell growth. The results of our second series are particularly significant in the development of this concept. Had we not included this second series involving a longer exposure time, then our conclusions from the first series would be that HPO had no effect upon tumor growth; this conclusion would have been virtually identical to those of Campbell,[4,5] Suit *et al.*,[15] McCredie *et al.*,[14] and Johnson *et al.*[11] But inspection of the distribution of metastases suggests that somewhere between 0.6 ATA oxygen (3 ATA air) and 1 ATA oxygen, there is a critical oxygen level or threshold, beyond which the manifestations of tumor growth inhibition after sufficient exposure time become statistically significant.

The inhibitory effects reported herein can be attributed to increased oxygen tensions rather than pressure *per se*. We found a similar distribution and number of metastases as well as no statistical difference in the primary tumor volume between the 1 ATA air control and 3 ATA air groups. Had the observed inhibitory effect been due to pressure, then we would have anticipated that there would be a similarity between the 3 ATA air and 3 ATA oxygen groups, or at least a statistically significant difference between tumor volume and distribution in the 3 ATA air as opposed to 1 ATA air. Thus our results are in line with those of Bean *et al.*[3] who reported little inhibition of tumor cell suspension viability upon exposure to 6 ATA air for 16 to 22 hours.

The similarity in mortality rate among all 4 groups might be explained on the

TABLE II

Author Year	Tumor Growth Inhibition	Animal Tumor (untreated survival)	Exposure: ATA	Exposure: P_IO_2 (mm. Hg)	Exposure: Length	Exposure: Number of Exposures	Oxygen Toxicity Signs	Parameters Studied (comments)
In Vitro								
Fischer and Andersen[8] 1926	Yes	Culture, Rous sarcoma, fibroblastoma	1–6	760–4,560	1–30 hr.	1 ×	—	Replant, record growth in 48 hours (12 hr. at 6 ATA lethal, 18 hr. at 3 ATA lethal)
Basset *et al.*[2] 1935	Yes	Tumor suspension, Rous sarcoma, 4 mouse tumors	1,000 1,800 4,000 6,000	"atm."	30 min.	1 ×	—	Transplant into animals, record takes (over 1,000 atm. fatal to tumor, Rous viral tumor most resistant)
Bean *et al.*[3] 1966	Yes	Tumor cell suspension, Ehrlich ascites	6	3,800	12–24 hr.	1 ×	—	Transplant into animals, record damaged cells in suspension, animal weight, abdominal distension, survival (inhibition with exposures 15 hr.)
In Vivo								
Fischer *et al.*[9] 1927	Yes	Mouse carcinoma	1.6–2	1,520	18–24 hr.	1 ×	Great numbers expired from pneumonia	Survival (27 per cent "favorable" cases if treated by 7th day after transplant)
Campbell and Cramer[4] 1928	No	Rat Jensen sarcoma Mouse carcinoma No. 63	0.6 0.6	456 456	2 wk. 2 wk.	Continuous Continuous	— —	Tumor weight, animal weight (Only in a 70 volume per cent oxygen atmosphere)
Fischer-Wasels[10] 1930	Yes	Mouse carcinoma, chondroma, adenocarcinoma	0.95	722	3–4 hr.	Daily	—	Survival (8–25 per cent cures)
De Almeida[7] 1934	Yes	Rat, fuso-cellular sarcoma (45 days)	27.7 6 6	2,052 4,560 4,560	3.5 hr. 1 hr. 2 hr.	1 × 1 × 1 ×	Avoided if animal was fasting before HPO	Survival (2nd series 23 per cent cure, 3rd series 100 per cent tumor destruction)
Campbell[5] 1937	No	Rat Walker carcinosarcoma (40–50 days) Mouse Bashford's tumor (36 days) Twort (60 days)	 5 4 4	 3,800 3,040 3,040	 1 hr. 1 hr. 1 hr.	1 × week for 7 weeks 1 × week for 5 weeks	20 per cent deaths each exposure 12 per cent deaths each exposure	Tumor size measurements (rate of growth the same for all tumors and controls)
Antopol *et al.*[1] 1961	Yes	Mouse Carcinoma 755 Sarcoma 180	5.7 (air) or 1.1 O_2	836	2–6 hr.	5 days per week 2–5 weeks	—	Tumor growth measurements and final tumor weight
Kluft and Boerema[13] 1964	Yes	Mouse mammary tumor (20 days)	3	2,280	2 hr.	2 × day until death	None	Tumor weight, survival, metastases (lung metastases definitely decrease)
Suit *et al.*[15] 1966	No	Mouse 6 different mammary tumors (60 days)	3	2,280	1 hr.	Daily, 5 × week for 6 weeks	Pulmonary changes	Tumor measurements or weight on final pressurization (some inhibition seems present to this author)
McCredie *et al.*[14] 1966	No metastatic increase	Mouse mammary tumor (>50 days)	3	2,280	30 min.	2 × day for 6 days	31 per cent convulsions; 14 per cent greater mortality in HPO group	Count of metastases 50 days after excising primary tumor, HPO given for 6 days before surgery (no HPO during time metastases were growing)
Johnson *et al.*[11] 1967	No	Mouse Cloudman S91 melanoma Leukemia L 12-10	3 3	2,280 2,280	30 min. 30 min.	20 × 20 ×	No No	Primary tumor volume, lung metastases Transplantation takes, survival

Key to abbreviations ATA = atmosphere absolute; P_IO_2 = pressure oxygen; HPO = hyperbaric oxygen.

basis that most animals died from respiratory problems due to lung metastases. The presence of pulmonary tumor cell metastases was accompanied by an interstitial pneumonia, the severity of which was not related to the number of tumor cells present. Even the fewer metastases seen in the 1 and 3 ATA oxygen groups resulted in the same amount of pulmonary disease and mortality. Other authors have noted this phenomenon of decreased pulmonary metastases but no difference in mortality rate.[13]

In evaluating our results, the explanations for the lessened tumor growth and spread with increased oxygen tensions is unknown. The oxygen may be exerting a direct toxic effect upon the tumor cell, acting at a site which is more sensitive to oxygen in a neoplastic cell. *In vitro* cell culture studies[2,3,8] would support this theory. Or with time, the tumor metabolism might change, making it more sensitive to oxygen at different periods of growth. Alternatively, oxygen may affect the tumor-host relationship in ways other than what is usually implied by "oxygen poisoning" of cells; any proliferating or rapidly metabolizing cell could be affected in ways as yet unknown. The immune reaction against the tumor might have been enhanced and thus slowed tumor growth. Any combination of these factors would also produce the observed inhibition.

Table II summarizes the conflicting reports in the literature concerning oxygen effects upon neoplastic growth. Two types of HPO studies have been tabulated; (1) HPO effects upon *in vitro* tumor growth and (2) HPO effects upon *in vivo* tumor growth. The difficulties encountered in the interpretation of this Table are manyfold and include the following points.

The susceptibility of an animal to oxygen toxicity (as experienced with mice) limits the time-pressure relationship for oxygen administration. The oxygen poisoning experienced by an animal exposed to an improper time-pressure relationship may cause uncontrolled secondary effects upon a tumor. Secondly, the criteria for noting an oxygen effect upon tumor growth vary with each author and range from tumor measurement (external and at autopsy) to tumor weight, animal weight, survival days, cell counts of ascitic fluid, viability of transplanted cells, to gross and microscopic metastasis data. As Kluft and Boerema[13] and Cohen *et al.*[6] point out, and our work substantiates, animal survival time may be unaltered despite the measurable decrease in tumor volume in exposed animals. Furthermore, different tumor systems may vary in the response to oxygen. Rapidly dividing cells might be more sensitive while slowly growing tumors could be relatively unaffected. Cohen *et al.*[6] point out that their best inhibition occurred during the log phase of growth of the Ehrlich ascites tumor. The inherent difficulties of tumor transplantation add to the complexity of the situation by including such variables as spontaneous regressions, tumor-host relationships, and changing degrees of malignancy.

The *in vitro* work is unanimous in obtaining tumor cell inhibition or even death, but in this type of study one can employ exposures prohibitive in animal work. The *in vivo* studies have never produced a significant increase in the tumor growth rate or metastatic spread in any of the systems studied.

CONCLUSION

The tumor and metastatic growth of the Walker carcinosarcoma can be inhibited by increased oxygen tensions in an adequate time-pressure relationship. A review of the literature further points out the fact that hyperbaric oxygen does not cause an increase in animal tumor growth or spread.

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RADIATION EFFECTS ON A CONDITIONAL CELL RENEWAL SYSTEM UNDER CONTINUOUS LOW DOSE-RATE EXPOSURE*

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OUR knowledge of the response of mammalian cell renewal systems to continuous low dose-rate gamma irradiation is limited to relatively few tissues, primarily the crypt population of the small intestine and the bone marrow.[21–26] The experimental evidence indicates that for such renewal tissues with relatively high rates of cell proliferation and cell loss, a steady state of cell population can be established under continuous irradiation, mainly by the production of sufficient numbers of mature cells to maintain function at a lower level of cell population. The factors which determine the state reached involve cellular radiosensitivity, which determines the rate of cell death, and compensatory cell proliferation, which determines the rate of cell birth.[21,22] In rapidly proliferating cell renewal systems under continuous irradiation, it appears that there is not a serious accumulation of sublethal damage from generation to generation[3,21] mainly due to the selection-out of damaged cells at division.[22]

In slowly dividing cell renewal systems, however, such selection-out of damaged cells would be expected to be less efficient, and it is important to know whether under continuous irradiation there is an accumulation of sublethal damage which could seriously affect cell proliferation, and thus the regenerative capacity of the tissue. The parenchymal cells of the liver comprise a conditional cell renewal system which has a very low rate of proliferation; while the tissue ordinarily undergoes little or no renewal, it may do so in response to a demand situation such as partial hepatectomy[27] (Fig. 1). An accumulation of cellular radiation damage during continuous exposure in cells with long intermitotic times could be expected to alter the kinetics of cellular proliferation during regeneration after partial hepatectomy, as for example, changes in proliferation rates, the size of the proliferating population, and the duration of

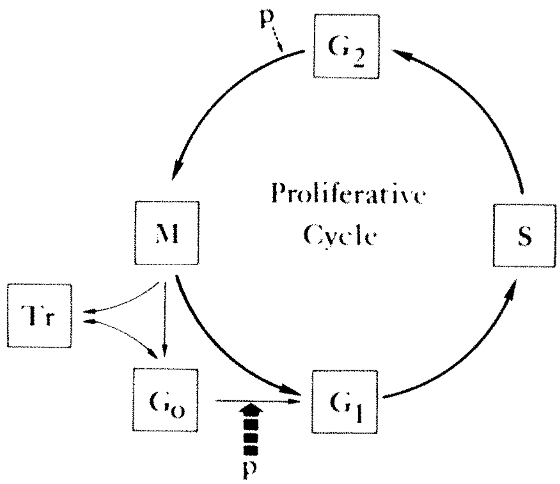

Fig. 1. Scheme of the compartments of the parenchymal cell proliferative system as a conditional renewal system based on the general model described by Quastler.[28] The proliferative cycle shows 4 phases (G_1 = presynthetic phase; S = synthesis phase; G_2 = postsynthetic phase; M = mitosis). The system contains a population of potentially proliferative cells (G_0) which produce at a low rate or only on stimulation (partial hepatectomy, p). Additional phases of Tr, transitional and mature cells, yield a basic scheme with at least 6 compartments.

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† Research was carried out while the author was an Advanced Fellow of Academic Radiology of the James Picker Foundation at the Department of Biophysics, Institute of Cancer Research, Surrey Branch, Belmont, Sutton, Surrey, England.

the cell cycle. The following studies examine the extent to which the parenchymal cell population of the rat liver as a conditional cell renewal system accumulates damage under continuous low dose-rate irradiation affecting cell proliferation and thus the speed and efficiency of regeneration. Since it has been shown that rats exposed to 50 rads/day can tolerate large doses for more than 16 weeks,[21] rats irradiated at 47 rads/day for 15 days were used in the present studies for examining parenchymal cell population kinetics at frequent intervals during the first 56 to 64 hours during regeneration.

MATERIALS AND METHODS

Details concerning the rats, continuous irradiation facility, technique of partial hepatectomy, labeled DNA precursor (tritiated thymidine), high resolution autoradiography, quantitative histology, and chromosome preparations have been described in previous publications.[11,13,16] These will be summarized briefly here, but for more detailed descriptions of the techniques and facilities used, the previous reports should be reviewed.

August strain male rats, 6–8 weeks old and weighing approximately 100 gm., were used. The control rats were housed in groups of 5 and the irradiated rats individually. All were fed food (M.R.C. Diet No. 41B) and water *ad libitum*.

The continuous gamma irradiation unit contained a central source of 5 curies of cesium 137 and was designed to irradiate a large number of animals at 47 rads/day.[29] The rats were given whole body irradiation continuously for approximately 23.5 hr./day; on completion of the exposure period, they were removed from the irradiation chamber for partial hepatectomy and not replaced until killed.

A standard technique for two-thirds partial hepatectomy was used.[19] Tritiated thymidine, specific activity 10–15 μc/mM (Radiochemical Centre, Amersham, Berkshire), in 100 μc/ml. solution of normal saline, was injected intraperitoneally, 0.5 μc/gm. body weight. Rats were killed (in groups of 2 or 4, as designated) with heavy ether anesthesia and cervical dislocation 1 hour or at frequent intervals after injection according to the experiment. A small portion (1 to 2 gm.) of the right lobe of the liver was fixed (ethanol-formalin-acetic acid) for 24 hours and stored in 70 per cent ethanol. Histologic sections (4–5 μ thick) obtained from wax-embedded tissue were prepared on gelatin-alum coated slides for high resolution autoradiography (liquid emulsion-dipping method). Slides were dipped in Ilford K-5 Nuclear emulsion (50°C.), dried, stored, and exposed at 4° C. for 2 or 3 weeks, according to the experiment. They were then developed in Kodak D19b developer, fixed in Johnson FixSol (16° C.), washed, dried, stained with hematoxylin and eosin and mounted.

All parenchymal cells were scored in representative cross sections of intact liver lobules, and percentage labeling and mitotic indices (in counts of 5,000 to 7,500 cells) and mean grain counts (in 50 cells) in the studies on cell proliferation in resting and regenerating liver, and the percentage of mitoses labeled in the studies on the parenchymal cell cycle were determined.[12,14]

For studies on radiation-induced chromosome aberrations, rats were irradiated continuously for periods up to 60 days. After exposure, they were partially hepatectomized and killed in groups of four 30 hours later, *i.e.*, during the wave of cell division. Liver tissue was minced in cold methanol-chloroform-proprionic acid fixative, and squash preparations prepared in 2 per cent acetic orcein stain. A minimum

Table I

PARENCHYMAL CELL PROLIFERATION IN NORMAL AND CONTINUOUSLY IRRADIATED RATS

Group	Percentage Labeling Index	Mean Grain Count (±1 *S.E.*)
Unirradiated	0.3	39.1±10.5
Irradiated	0.3	37.3± 9.1

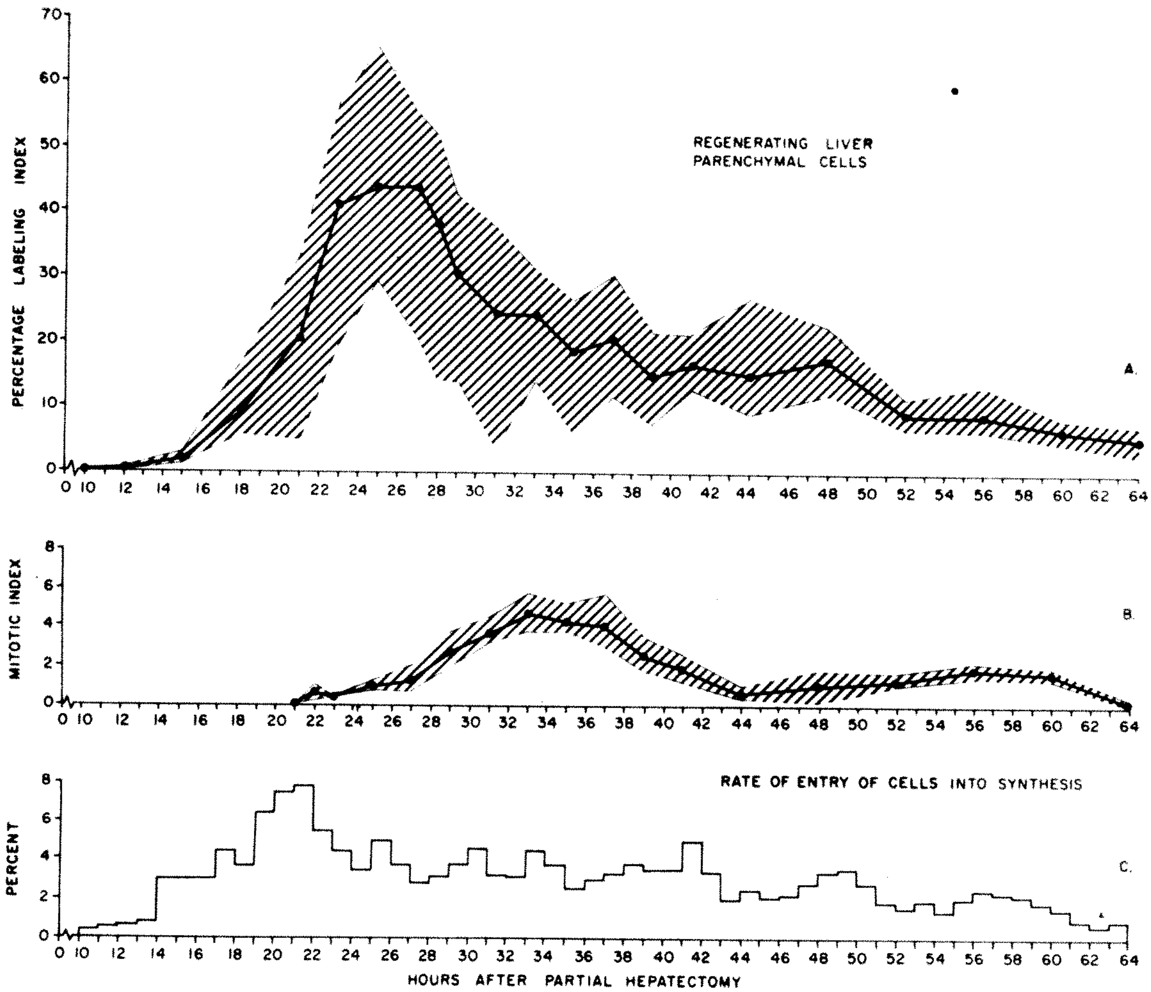

FIG. 2. (*A*) The temporal pattern of incorporation of tritiated thymidine into proliferating parenchymal cell nuclei in the rat liver at frequent intervals during the 64 hours following partial hepatectomy. The mean values and range for 4 rats at each sacrifice interval are shown. (*B*) The temporal pattern of parenchymal cell mitoses in the rat liver at frequent intervals during the 64 hours following partial hepatectomy. The mean values and range for 4 rats at each sacrifice interval are shown. (*C*) Histogram of the hourly rate of entry of cells into synthesis after partial hepatectomy determined from the labeling and mitotic index data. The duration of mitosis is 1 hour and of synthesis, 8.0 hours.

of 100 to 150 mitoses per slide were scored, and anaphase-telophase aberrations per 100 mitoses were determined in irradiated and control livers.[4,5,11]

RESULTS

RESTING LIVER

Mitotic indices, 1 hour percentage labeling indices, and mean grain counts in parenchymal cells in the normal and continuously irradiated liver were determined (Table 1). Cells in division were extremely rare in both groups and appeared normal. Percentage labeling indices and mean grain counts were not significantly different between unirradiated and irradiated rats.

REGENERATING LIVER

Unirradiated rats. The pattern of 1 hour percentage labeling indices at frequent intervals during the 64 hours after partial hepatectomy in 92 rats is shown in Figure 2*A*. At 12 hours, labeled liver cells were first seen in the region of the portal triads; there

was a rapid rise in labeling indices to 44 per cent at 25 hours followed by a gradual fall during the next 40 hours. A second and smaller rise occurred between 44 and 52 hours. Elevated levels persisted for a number of days, returning to normal after 2 to 3 weeks when regeneration was complete. Cell division began at 21 hours after partial hepatectomy (Fig. 2*B*). The mitotic index rose rapidly to 5 per cent by 33 hours, and then declined; a second smaller rise occurred between 52 and 60 hours. Mitotic indices remained elevated for a few days, and returned to normal levels by 2 weeks. Waves of cells in division followed those in DNA synthesis by approximately 8 hours; allowing for this interval there were 5 to 10 times as many cells labeled as in mitosis. Figure 2*C* is a histogram of the hourly rate of entry of cells into DNA synthesis during

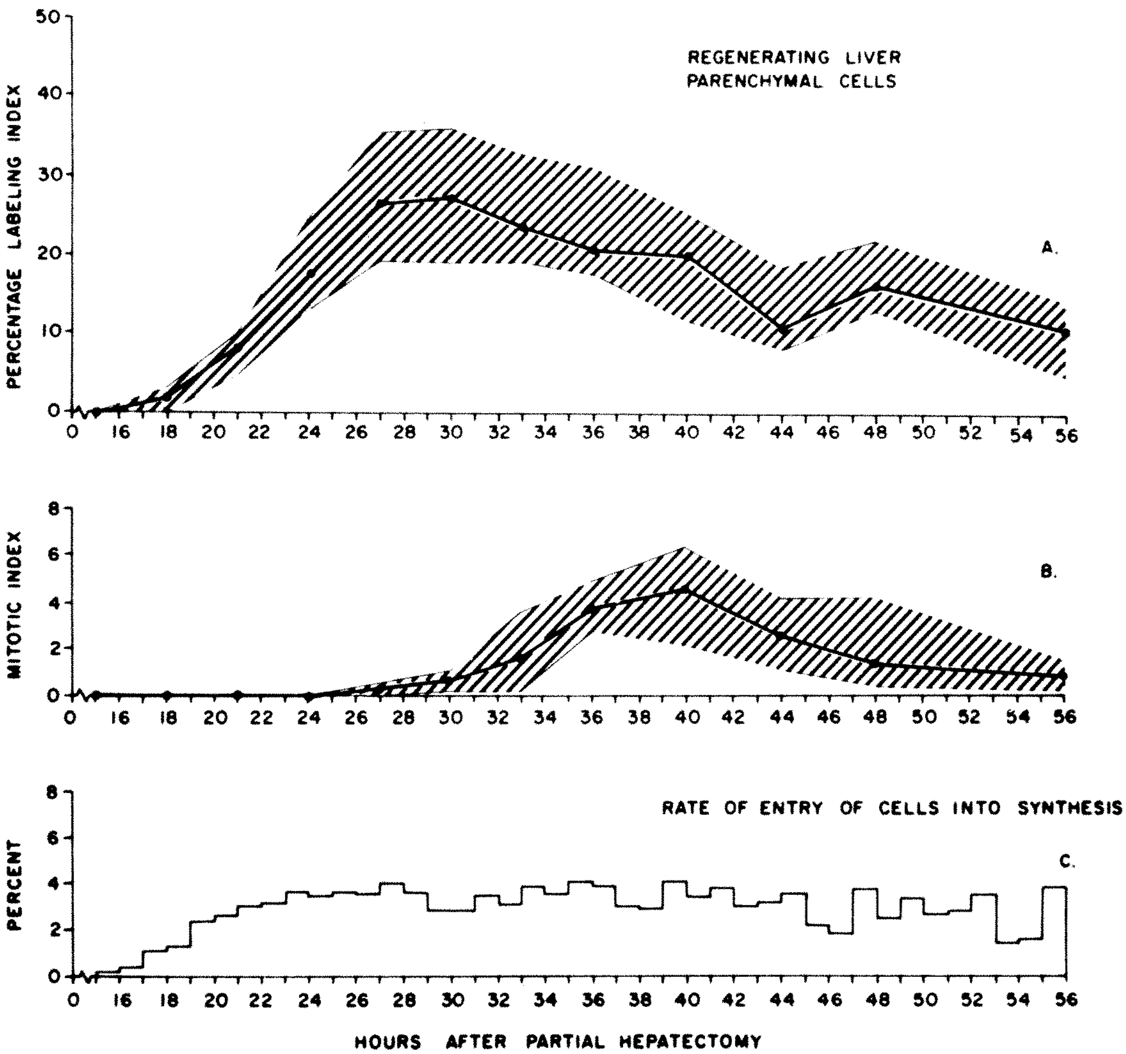

Fig. 3. (*A*) The temporal pattern of DNA synthesis in proliferating parenchymal cells in the regenerating liver after prior continuous irradiation at 47 rads/day for 15 days. The mean values and range for 4 rats at each sacrifice interval are shown. (*B*) The temporal pattern of parenchymal cell division in the regenerating liver after continuous exposure to 47 rads/day for 15 days. The mean values and range for 4 rats at each sacrifice interval are shown. (*C*) Hourly rate of entry of parenchymal cells into DNA synthesis during the 56 hours of regeneration after partial hepatectomy in rats continuously irradiated at 47 rads/day for 15 days; the duration of mitosis is 1 hour and of synthesis, 7.0 hours.

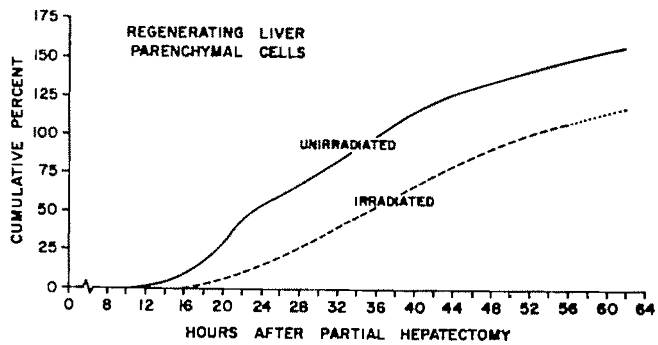

FIG. 4. Cumulative percentage entry of proliferating parenchymal cells into DNA synthesis during the 64 hours of liver regeneration after partial hepatectomy in unirradiated August rats, and during the 56 hours of liver regeneration in rats previously exposed to 47 rads/day for 15 days.

the initial 64 hours of regeneration calculated from the mitotic and labeling index data corrected for the increasing mass of the liver remnant.[15,18,32] The duration of DNA synthesis was taken as 8.0 hours based on percentage labeled mitoses data (Fig. 6*B*). Rather than a burst of proliferative activity in a large population of hepatocytes, there was almost a steady passage of cells through synthesis at a rate of approximately 4 per cent/hr. until 50 hours, followed by a gradual decline. By 64 hours, most of the cells necessary for restoring a very large proportion of the hepatic cell deficit had entered synthesis.

Irradiated rats. The pattern of 1 hour percentage labeling indices and mitotic indices of parenchymal cells during the 56 hours after partial hepatectomy and prior continuous irradiation at 47 rads/day for 15 days are illustrated in Figure 3, *A* and *B*. Prior continuous irradiation delayed the onset of cell proliferation and cell division after partial hepatectomy by approximately 6 to 10 hours. Waves of labeled cells and mitoses were broader than in the unirradiated animals, and peaks were lower, separated by approximately 10 hours, and declined more slowly. Taking the duration of synthesis at 7.0 hours, based on percentage labeled mitoses curves (Fig. 6*C*), and correcting for the interval growth of the liver mass,[15,18,32] the rate of entry of cells into DNA synthesis was decreased to approximately 3 per cent/hr. after irradiation, and the gradual decline occurred approximately 8 hours later than in control animals (Fig. 3*C*).

By 56 hours, the cumulative hourly labeling and mitotic indices, *i.e.*, the fraction of hepatocytes proliferating, after irradiation were both 20 per cent below normal values (Fig. 4). While the synthesis-mitosis sequence was efficient in the control and irradiated groups, the rate was decreased and fewer cells proliferated after irradiation. Allowing for a gradual decline in rates of proliferation after 56 hours, the unirradiated rats replaced a large fraction of the liver cell deficit by 72 hours, while the irradiated rats required more than 100 hours for equivalent cell restoration.

The mean grain counts at different labeling periods during regeneration varied widely and were higher in the irradiated animals (Fig. 5). This may have been due to increased polyploidy or a greater availability of tritiated thymidine in the irradiated rat.[29,34]

Parenchymal cell cycle during regeneration. Following flash-labeling with tritiated thymidine, the relationship between the fraction of mitoses labeled and time may be used for estimating the duration of the 4 main phases of the cell cycle[20] in a proliferating cell population.[28,30] The first wave of labeled mitoses is often well defined, and in most cell populations, the variation in the presynthetic (G_1) phase is greater than the variation in the postsynthetic (G_2),

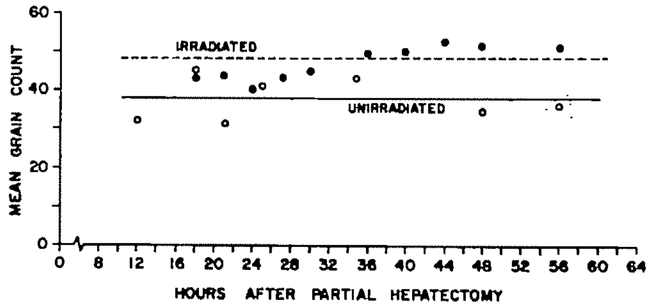

Fig. 5. Mean grain counts over parenchymal cell nuclei in DNA synthesis at frequent intervals after partial hepatectomy in unirradiated rats and in rats continuously exposed to 47 rads/day for 15 days.

synthesis (S) or mitotic (M) phases. On graphic analysis of an experimental curve, the 50 per cent points of the first wave of labeled mitoses measure the mean duration of the S phase (Fig. 6*A*). The duration of the G_2+M/2 compound is measured on the abscissa from the time of injection (0 hr.) to the midpoint of the ascending limb, whereas the duration of mitosis may be roughly estimated as its rise-time. Since by this method, the cycle time (T_c) and the duration of the G_1 phase can only be determined for cells dividing for two or more times, only the durations of the G_2, M and S phases of proliferating parenchymal cells in the regenerating liver can be measured with any precision.

Tritiated thymidine was injected at 20 hours (unirradiated rats) or 30 hours (irradiated rats) after partial hepatectomy; animals were killed in pairs at frequent intervals, and the fraction of mitoses labeled with time after injection was scored in each group. The theoretical experimental curve, and unirradiated and irradiated curves for regenerating parenchymal cells are shown in Figure 6, *A*, *B* and *C*. The durations of the G_2+M/2 and S phases of the proliferating parenchymal cells, and the approximate values for the G_1 phase and the cell cycle, T_c, for cells dividing for a second time are listed in Table II. Normally, the shortest duration of the G_2 period was 2.5 hours, the mean duration of the G_2+M/2 period, 3.0 hours, and of S, 8.0 hours. Very approximate durations for

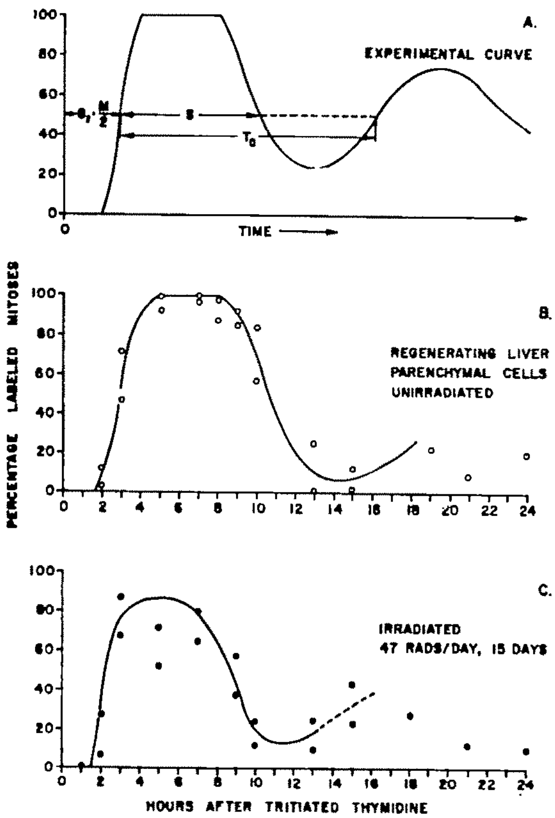

Fig. 6. Percentage labeled mitoses curves (*A*) for a cell renewal system, (*B*) for proliferating parenchymal cells in the regenerating liver of unirradiated rats, and (*C*) after continuous irradiation at 47 rads/day for 15 days. The time of injection of tritiated thymidine (0 hour in *A*) corresponds to 20 hours and 30 hours after partial hepatectomy in control and irradiated animals, respectively. Each point represents 1 animal.

the G_1 phase and T_c for cells dividing more than once were 3.5 hours and 15.0 hours, respectively. After irradiation, the curve was similar to that of the unirradiated animals, but with more scatter of experimental points. There was a shortening of the duration of S by 1.0 hour, a decrease in the mean duration of $G_2+M/2$ by 0.5 hour, of G_1 by 0.5 hour, and possibly a decrease in mean T_c by 2.0 hours.

Chromosome aberrations. Figure 7 illustrates the number of spontaneous and radiation-induced anaphase-telophase aberrations per 100 liver cell mitoses scored 30 hours after partial hepatectomy. There was little change in control values during this period, although it has been shown that the number of spontaneous aberrations increased with age, from approximately 10 per cent in 6 week old rats to 15 per cent in 23 week old animals.[10,11] About 10 per cent of the aberrations observed in irradiated animals were considered to be spontaneously produced. After exposure to 47 rads/day there was a rapid rise to approximately 30 aberrant cells/100 mitoses by the third week. After the initial rise, however, the frequency did not increase, but remained constant with time and accumulated dose. Polyploid cells had fewer aberrations despite the greater numbers of chromosomes.

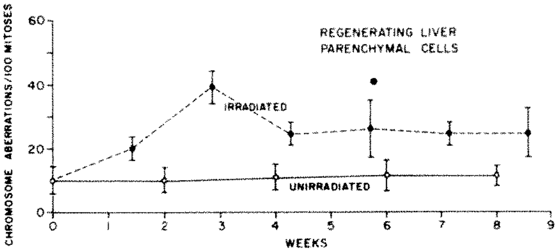

Fig. 7. The effect of duration of exposure on the number of chromosome aberrations in proliferating parenchymal cells during liver regeneration in rats continuously exposed to 47 rads is shown. The mean values ± 1 standard error of the mean at each sacrifice interval are given.

DISCUSSION

In rapidly dividing cell renewal systems under continuous low dose-rate irradiation, there is an effective selection-out of damaged cells as well as repair of sublethal damage affecting cell proliferation and thus the speed and efficiency of regeneration. In a more slowly dividing or conditional cell renewal system, such as the liver, there appears to be apparently some intracellular repair or elimination of cellular radiation damage.[5–8,17] If radiation produced lethal, nonreparable effects on cells with long intermitotic times, then conditional renewal tissues would accumulate cellular damage impairing adequate proliferative capacity. However, the experimental evidence indicates that the pattern of cell proliferation after partial hepatectomy was relatively little disturbed by prior exposure to a dose rate of 47 rads/day in spite of the accumulation of relatively large radiation doses and in the presence of considerable chromosomal injury.

Under continuous irradiation, the turnover time of the parenchymal cell population, taking the duration of DNA synthesis as 7.0 to 8.0 hours, remained unchanged at 100 to 150 days, provided all cells comprised the proliferative pool and divided. While the grain count distribution varied widely, the elevated mean grain counts in irradiated cells may have been due, in part, to the development of polyploid hepatocytes in the growing rat,[1,2] and to the production of polyploid cells as a result of radiation injury.[29,33]

However, following continuous exposure at 47 rads/day, parenchymal cell prolifera-

Table II

PHASES OF PARENCHYMAL CELL CYCLE IN REGENERATING RAT LIVER AFTER CONTINUOUS IRRADIATION AT 47 RADS/DAY FOR 15 DAYS

Phase	Unirradiated (hr.)	Irradiated (hr.)
G_2	2.5	2.0
$G_2+M/2$	3.0	2.5
S	8.0	7.0
G_1	~3.5	~3.0
T_c	~15.0	~13.0

tion could be initiated and maintained after partial hepatectomy, but at a decreased rate, and in spite of having accumulated chromosome damage. Prior irradiation delayed the onset of DNA synthesis and cell division, decreased the numbers of cells proliferating, decreased the rate of entry of cells into DNA synthesis, and increased the over-all period of cell proliferation during regeneration. There was a slight shortening of the duration of the S and $G_2+M/2$ phases in the proliferating cell population and an increase in the number of observable chromosome aberrations and of polyploid parenchymal cells. However, the pattern of cell proliferation after partial hepatectomy was relatively little disturbed by continuous irradiation, even by large accumulated doses; while the efficiency of cell proliferation was reduced, irradiated parenchymal cells remained capable of dividing a few times to replace a very large proportion of the cell deficit within approximately 1 week.

The accumulation of nonlethal cellular damage under continuous irradiation in the stem cells of a conditional renewal tissue is one of the major factors affecting the regenerative capacity of the precursor cell population. A mechanism influencing the speed and efficiency of regeneration following radiation injury and compensating for the decreased rate of entry of cells into DNA synthesis and mitosis would be speeding up of the cell cycle. The data indicate that under continuous exposure, the durations of the S and $G_2 + M/2$ periods were shortened by 1.0 and 0.5 hours respectively, thereby increasing the rate of proliferation at the lower population level. Thus, in the unirradiated regenerating liver, most cells divided only once, and some twice, to restore a large fraction of the original cell numbers within 3 days. After irradiation, fewer cells participated in the regenerative process and an increased number of division cycles was necessary. Damaged cells which have lost their capacity for indefinite division apparently could still divide several times to replace the cell deficit.

A speeding-up of cells through the S and G_2 compartments would also compensate for the radiation inhibition of the onset of cell proliferation after partial hepatectomy, and for the decrease in the cell population participating in the regeneration. The prolonged regenerative process after irradiation would permit more divisions in the decreased proliferating cell population, indicating that biochemical pathways necessary for rapid cell proliferation after partial hepatectomy remain operative for a longer period in the irradiated animal.

Cellular radiation injury, such as polyploidy and chromosome damage, accumulated under continuous exposure would also be major factors affecting the proliferative capacity of the precursor cell population and its ability to deal with chronic stress. The decreased proliferation rate could have resulted, in part, from radiation-induced polyploidy. Mean grain counts were generally higher in irradiated animals, and this may have been due to increased polyploidy or to a greater availability of tritiated thymidine to proliferating cells.[13,29,34]

At 47 rads/day for up to 60 days, after an initial rise in the yield of chromosome aberrations, the frequency remained constant with time after the the second week. Such a steady state condition, in which the loss or repair of intracellular damage equals the rate of production, has been observed in *Tradescantia* and *Vicia faba* under continuous low dose-rate exposure.[9,34] Repair of initial radiation damage is known to have occurred, since in recent studies[17] on effects of exposure to dose-rates from 16 rads to 375 rads/day, it was shown that the number of chromosome aberrations was dose-rate dependent. The constant incidence of chromosome aberrations with increased duration of exposure indicated that long-term repair of chromosome damage occurred with the passage of time, either by repair of intracellular damage during interphase or by the selection-out of damaged cells by cell division.[5–8,11,17,31] As far as the repair of chromosome injury under continuous irradiation in a condi-

tional cell renewal system, such as the non-proliferating liver, is concerned, the most recent exposure appears to be most effective, and repair of cellular radiation damage can occur in tissues with normally low rates of cell proliferation.

CONCLUSIONS

The response of the cell renewal systems of the body to continuous low dose-rate irradiation appears to be a consequence primarily of the difference in dose-rate at which a steady or near-steady state of cell population can be established at a lower population level and can maintain essential function.[21,22] It appears that accumulation of cellular radiation damage from generation to generation is not a very significant effect in rapidly dividing cell systems, such as bone marrow, due to the selection-out of damaged cells at division. In conditional cell renewal systems under continuous irradiation, such as the slowly dividing liver cell population, the selection-out of damaged cells will be less efficient. However, in spite of the accumulation of relatively large radiation doses and in the presence of considerable cellular radiation damage, the pattern of cell proliferation during regeneration after partial hepatectomy does not appear to be seriously affected by prior continuous exposure. Such tissues with cells of long intermitotic times apparently can accumulate very large radiation doses under continuous irradiation and still retain adequate proliferative capacity in a demand situation, such as the liver after partial hepatectomy. Homeostatic mechanisms which influence the speed and efficiency of regeneration following injury under continuous irradiation apparently can operate effectively to reduce the deleterious effects and to repair radiation damage, either by intracellular mechanisms or by the selection-out of damaged cells at mitosis.

These experiments give only limited information on the accumulation of chromosome and other nonlethal cellular damage under continuous irradiation in cells of only one conditional renewal system. Much more work needs to be done, particularly on the sensitivity throughout the cell cycle in such slowly dividing cells with long intermitotic periods, and on mechanisms of intracellular repair of initial radiation damage, before a better understanding of cellular response and cell population kinetics in conditional renewal systems under continuous irradiation can be had.

SUMMARY

The pattern of cell proliferation after partial hepatectomy was relatively little disturbed by prior exposure to a dose-rate of 47 rads/day in spite of the accumulation of large radiation doses and in the presence of considerable chromosome injury. There was a delay in the onset of DNA synthesis and mitosis, a decrease in the rate of entry of cells into synthesis and division, a decrease in the number of cells participating in the regenerative process, an increase in the duration of cell proliferation during regeneration, an increase in chromosome aberrations and polyploid cells, and a speeding-up of cells through the S and $G_2+M/2$ compartments.

These changes are considered in terms of cellular response and cell population kinetics of a slowly dividing conditional renewal system under continuous irradiation, and the possible extent to which compensatory and repair mechanisms can operate are discussed.

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Table III

RADIATION EFFECTS ON STEM CELL SURVIVAL IN THE BONE MARROW OF MOUSE

	Control	Time After Conditioning Dose				
		3	18	24	36	60
D_0	110	135*	85*	105	50*	130

* Significantly different from control value at $p<0.01$.

which are resting out of cycle. When the tumor gets larger, its growth rate appears to be slower than can be explained on the basis of the number of cells in division. There must be a certain number of cells which migrate or die; and (c) in the autoradiographs of large tumors, the labeling is heterogeneous even after multiple injections. Throughout the tumor at 20 days there are zones where the labeling is high and nearby there are zones where the number of labeled cells is low or zero.

This appearance suggests that there are regions where the cells are at rest and nearby zones where the cells are in active proliferation. It is possible, but not certain, that the zones of active proliferation are centered around vessels. During the growth of the tumor, as the growth fraction diminishes, it is likely that the proportion of the tumor, where the cells are at rest, increases.

This could be of practical importance if the sensitivity of the resting cells to a therapeutic agent is different from that of dividing cells.

Little is known about the radiosensitivity of these resting cells and their behavior after irradiation. Their reaction to chemotherapy may also be different. Another question arises: Are these cells, which do not divide, unable to go into mitosis, or are they able to divide following an appropriate stimulus as would be suggested by the results of Baserga and Lisco?[2]

II. EFFECTS OF A SINGLE EXPOSURE ON THE RADIOSENSITIVITY OF A TISSUE

A single radiation exposure may lead to a change in the structure of the cell population in the course of the next few hours or days through the temporary arrest of some cells in different stages of the cell cycle. This change in population structure may have an over-all effect on the radiosensitivity of the residual irradiated population. *In vitro*, Elkind *et al.*[9] have shown that the variations in radiosensitivity observed after the first irradiation are due in part to processes related to intracellular restoration and in part to the progression through the cell cycle of the surviving cells. By cooling the cells in order to arrest their progression in the cycle, they were able to differentiate the two phenomena.

In vivo, Kallman[16] has shown a significant variation in the sensitivity of animals submitted to a second radiation exposure at various times following an earlier exposure. Till and McCulloch[34,35] have also observed a variation in the sensitivity of the bone marrow of mice. We have recently shown, with E. L. Alpen and H. S. Kaplan,[11] that whole body irradiation of the mouse with 250 rads leads to important modifications in the kinetics of the marrow population and that significant variations in the radiosensitivity of marrow stem cells also occur (Table III). This latter finding was established by use of the splenic nodule count for cells of endogenous origin. If such changes occur in a tumor and if the chronology of events differs in the tumor and in the surrounding normal tissues, the effect of a fractionated irradiation would vary with the interval between the two exposures. It is conceivable that a proper interval between exposures can increase the effects of irradiation on some tissues and decrease them on others.

The problem, then, is how to obtain for a

patient the data which would enable the choice of the best fractionation. The kinetics of irradiated normal human tissues will probably become known during the next few years and it is reasonable to hope that this information can be extrapolated from one human being to another. For tumor cells, the problem is much more difficult. It is possible that some correlation will be found between the characteristics of the tumor, *e.g.*, the growth rate or the pathologic type and the parameters of cell kinetics after irradiation. Another possibility is that techniques of the study of kinetics will be found which do not involve the injection of H^3-thymidine in patients, such as the study of multiple biopsy specimens after *in vitro* incubation and organotypic tissue culture, or the use of IUDR. Although the problem is obviously complex, it does not appear impossible to solve.

III. INFLUENCE OF SINGLE IRRADIATION ON TUMOR CELL KINETICS

Irradiation may modify the rhythm of the cellular kinetics of tissues. Many studies in the last few years, notably those of Lamerton *et al.*,[22] have been devoted to the effects of repeated or continuous exposure to radiation of normal tissues. It has been observed that there is an increase in the number of proliferating cells in certain tissues as well as a minor shortening of the cell cycle.

The effect of repeated exposures on cell kinetics is very important because the result of fractionated irradiation depends on the growth activity of the tumor between the exposures. This has been the subject of relatively few investigations. Some authors have thought of the cell population of cancerous tissue as being autonomous and that the kinetics are little affected by irradiation. This view is, however, not based upon experimental facts.

We have studied and compared the cell cycle in an irradiated and a nonirradiated region in the tumors of our 2 cases. The irradiated portion of the tumor received 250 r 30 hours before the injection of radioactive thymidine; the cell cycle appeared to be shortened. One must be careful in interpreting these data because of the small number of points. In addition, the labeling index has not changed, even though at least half of the cells must have been made nonviable by the irradiation. This suggests an elevation of the growth fraction.

In the mouse tumor, we have not found any significant shortening of the cell cycle after irradiation, but this may be due to the fact that the cycle was already short before irradiation. On the other hand, we have been able to demonstrate a significant increase in the growth rate of the tumor based on *in vivo* measurement of tumor volume.[23] This study was performed on the same NCTC fibrosarcoma of the C_3H mouse as was used in the previously discussed tumor cell kinetics study. In this tumor, the growth rate slowly decreased with age.

The growth rate of the surviving cells in the irradiated tumors was evaluated by analysis of the change in size of the tumor. This change is caused by many phenomena occurring simultaneously: the cells killed or made nonviable by the irradiation slowly disappear. Some of them divide 2 or 3 times before lysis. The removal of the nonviable cells and their progeny is therefore a slow process, which may take for this tumor 10 to 12 days. During this interval the surviving cells proliferate. After the total removal of the nonviable cells, that is after the 10th day following irradiation, the tumor is composed only of the progeny of the surviving cells. If the initial number of surviving cells were known it would be possible to calculate their growth during the period of removal of dead cells (Fig. 1).

For the tumor used in this study, it is possible to measure the dose-survival curve by the clonal method of Puck. When the cells are irradiated in air the D_0 is 210 rads and the extrapolation number $n=2.3$. This corresponds for these cells to a D_0 of 630 rads in anoxic condition. A second estimate of the D_0 has been made *in vivo* by measuring the curative dose for 50 per cent of tumors irradiated *in vivo*. To avoid oxygen effects the tumors were irradiated under

anoxic conditions by isolating the tumor with a clamp. After 3,000 rads, 30 per cent of the tumors underwent a transitory regression ranging from 8 to 22 days. Fifteen per cent became palpable again. After 5,000 rads, more than 80 per cent of the tumors disappeared in about 10 days and 55 per cent were definitely cured. After 7,000 rads, all the tumors disappeared in about 8 to 14 days.

Relating the proportion of cured tumors to the dose, a regular sigmoid curve is obtained. Approximately 50 per cent of the tumors are cured by a dose of 4,500 rads. Knowing that at the time of irradiation there are 30 million cells in the tumor, it is possible to calculate the cell survival by assuming that the number of cells necessary to establish a recurrence is the same as the number needed to induce a tumor in 50 per cent of the animals (TD_{50}) *i.e.* 30,000 cells. This calculation gives a value for D_0 of 670 rads, but is open to discussion since the assumption that the number of cells necessary for a recurrence is the same as that of the TD_{50} may not be valid. If the presence of a large number of irradiated cells lowers the number of surviving cells necessary to induce a recurrence, the D_0 *in vivo* would be smaller than *in vitro*.

Assuming for D_0 *in vivo*, a value of 650 rads, the study shows that the growth of the surviving cells in an irradiated tumor is more rapid than for the cell population of a nonirradiated tumor *of the same age*. This increase in growth rate would be greater if the D_0 were smaller *in vivo* than *in vitro*. The acceleration of the growth rate would come about if the death of an increased proportion of cells in the tumor permitted an increase in the multiplication rate for the remaining cells. This increase could be due to a shorter cell cycle or to a higher growth fraction. The duration of the cell cycle in these irradiated tumors is unchanged. It is therefore likely that the growth fraction is higher. The increase in growth rate would come to pass if, for progressively smaller surviving populations, the growth fraction of the surviving cells became progressively higher.

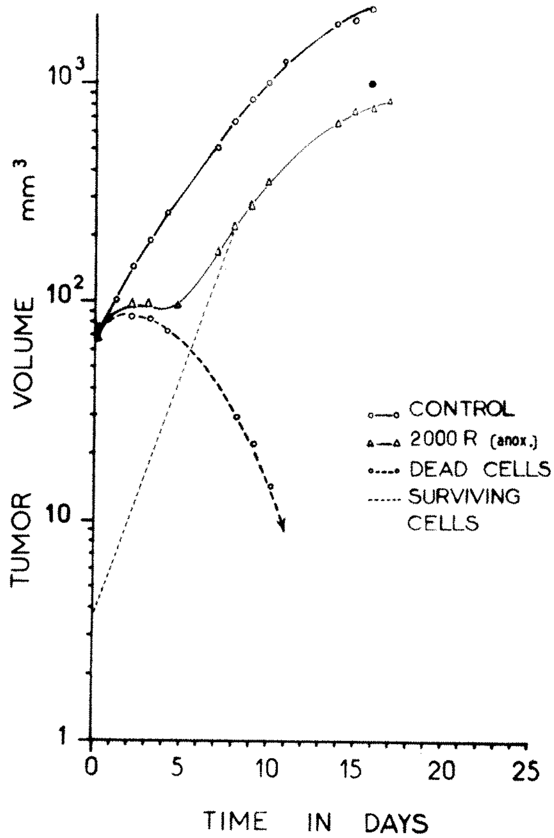

Fig. 1. The evolution of the size of an irradiated tumor is caused by 2 phenomena: the removal of nonviable cells and the proliferation of surviving cells. After 7,000 rads, all the cells are killed and the evolution of the volume of the tumor indicates the rate of elimination of dead cells.

In vivo, the D_0 of the NCTC 2,472 tumor cells is 650 rads under strictly anoxic conditions. Therefore, when a population of tumor cells receives, under anoxic conditions, a dose of 2,000 rads, 4.6 per cent of the cells survive.

Almost all killed cells are eliminated by the 10th day. At this time, the population of cells which has received 2,000 rads is almost completely composed of the progress of surviving cells. Interpolation between the volume of surviving cells at Day 0 (day of irradiation) which is 4.6 per cent and the volume of the tumor at Day 10 allows the mean growth rate of surviving cells to be calculated. This is more rapid than that of the cells of control tumors.

—○—○— growth curve of control NCTC 2,472 tumors; —△—△—△— growth curve of irradiated tumors (2,000 r at Day 0 under anoxic conditions); — —○— —○— — evolution of the volume of irradiated tumors (7,000 rads at Day 0).

The comparison of the growth of the surviving cells in an irradiated tumor with the growth of much smaller control tumors

composed of the same number of viable cells shows that the growth of the irradiated surviving cells is a little slower. This is easy to note when comparing the growth of palpable tumors. A computation assuming the value of the D_0 to be 650 rads shows that this is also probable during the initial phase of the growth of the recurrent tumor.

Thus, the surviving cells in a tumor which has been irradiated grow faster than the cells of an unirradiated control tumor of equal age and size, but more slowly than the cells of a tumor composed of an equal number of viable cells. These facts must have a complex interpretation. They show that a tumor may not be considered as a population of autonomous cells, multiplying according to their characteristic period and independent of outside influence.

Is it possible to extrapolate these data to clinical radiation therapy? To do so, it would first be necessary to ensure that these modifications of growth rate were the same after many exposures. If this were true, a constant interval between sessions would not be logical, and perhaps a shortening of this interval at the end of treatment would be advisable. Such a conclusion is certainly premature, and is given simply to illustrate what practical directions could be drawn from this kind of study after information on other types of experimental tumors has been obtained.

Furthermore, many other factors should be taken into account in choosing the best fractionation, such as the radiosensitivity of normal tissues and the oxygen effect.

Our experiments show that a relatively high proportion (of the order of few per cent) of the cells of these tumors is anoxic. A similar finding has been made in previous studies.[28] The curability of tumors by radiotherapy may appear surprising in view of these findings, but it seems that during fractionated radiotherapy, the same cell may not remain anoxic throughout the course of the treatment and that the number, or even the proportion, of anoxic cells may gradually decrease during the treatment. This factor may be of paramount importance in choosing the best fractionation.[31,33]

CONCLUSION

Recent study has shown that the radiosensitivity of a cell varies during the course of the cell cycle. The kinetics of cell proliferation of a tumor should, therefore, be related to its radiosensitivity. This fact emphasizes the need of such studies in human and experimental tumors. Furthermore, the temporary arrest of the cell cycle following irradiation results in a variation of the radiosensitivity of the tissue which is being studied and measured. This and other factors, such as the variation of the growth rate of the surviving cells in an irradiated tissue, should be taken into account in the choice of the best fractionation. Study of all these factors in experimental, as well as in human tumors, will necessitate considerable future investigation to provide a rational basis for the development of radiotherapeutic procedures.

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DACRYOCYSTOGRAPHY*

THE USE OF SINOGRAFIN FOR VISUALIZATION OF THE NASOLACRIMAL PASSAGES

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ROENTGENOGRAPHIC study of the nasolacrimal system following instillation of various opaque media has been well documented[1–5,9–14,17] as being of definite value in complementing information obtained by the usual clinical procedures. The injection method was first reported in 1909 by A. E. Ewing[8] who used a bismuth preparation to demonstrate a lacrimal abscess. Since then, the lacrimal passages have been studied roentgenographically using various oily opaque media such as iodinated poppy-seed oil (lipiodol), ethyl diiodostearates (ethiodol and neo-hydriol) and ethyl iodophenylundecylate (pantopaque). If the oily materials are inadvertently extravasated into the surrounding tissues they remain for long periods of time. In addition, they tend to plug the ducts, especially if they are pathologic. They can also cause false-appearing polycystic sacs when they fail to fill the entire sac because of emulsification of the oil which is only slightly miscible with tears. Their high viscosity also requires greater pressure for injection, resulting in more frequent backflow through the upper canaliculus, preventing the passage into narrower sections, thus often hindering the true and exact location of a stenosis. In addition, oily materials are nonphysiologic and may give less information as to physiologic efficiency of the lacrimal passages.

In order to permit more physiologic conditions, the more liquid aqueous contrast substances have been used. The requirements are that they be water soluble; that their voscosity and pH approach those of tears (pH 7.0 to 7.5);[18] and when used in adequate concentration produce an image which is of sufficient contrast for roentgenographic examinations. Too highly concentrated solutions may offer no advantage in film interpretation and may, in fact, result in local irritation caused by the more concentrated solutions of iodine. Aqueous contrast substances can be injected under lower pressure than oily substances because they are homogeneous, more liquid, and miscible with body fluids, especially the tears. Their low surface tension and low viscosity are of particular importance since the latter is responsible for easy penetration into the small canaliculi and for reduced internal friction. Thus they should produce a more accurate picture of the pathologic conditions of the lacrimal passages than do oily solutions. A further advantage of these media is that patients can taste the aqueous materials immediately because they are bitter when the opaque medium goes through a normal sac promptly into the nasal meatus, indicating to the diagnostician that the duct is immediately patent.

Certain water soluble materials, such as sodium acetrizoate and sodium diatrizoate, have the disadvantage that sodium salts are irritating when they escape into the surrounding soft tissues. However, the methylglucamine diatrizoates are less irritating if they should extravasate into the soft tissues. Sinografin* contains 40 per cent methylglucamine diatrizoate (renografin) and 20 per cent methylglucamine iodipamide (cholografin). The iodine content of sinografin is 38 per cent (bound) making the concentration of iodine quite adequate for visualization. The pH of sinografin, being 7.2 to 7.6, is close to that of tears. Thus sinografin meets all the above requirements as to nonirritability, homo-

* Methylglucamine diatrizoate (40%) and methylglucamine iodipamide (20%). E. R. Squibb & Sons, New York, New York.

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geneity, low viscosity and miscibility with body fluids including the tears.

TECHNIQUE

The ideal method would be to instill a few drops of an opaque medium into the lower orbital cul-de-sac and follow its movements through the lacrimal passages. Unfortunately the dilution of the opaque substances by tears prevents adequate concentration in the lacrimal passages for the usual static roentgenogram. It is, therefore, necessary to resort to direct injection into the canaliculus and this procedure requires considerable pressure. The physiologic conduction through the nasolacrimal duct is very slow when oily media have been used. In spite of the hypersecretions resulting from injection, oily contrast substances can be found in the sac up to 30 minutes after the injection in normal persons.[12] On the other hand, the physiologic aqueous media (sinografin) will normally clear within 15 to 30 seconds and enter the nasal fossa immediately, where it will result in a bitter taste.

No premedication is necessary. Proparacaine HCl 0.5 per cent (ophthetic*) is the local anesthetic of choice. Any fluid contained in the lacrimal sac is expressed with a finger pressed against the side of the nose. The lower lacrimal punctum is dilated with a blunt Nettleship punctum dilator.[15] The dilator is first held vertically and introduced inferiorly. It is then rotated through 90° toward the nose, while the canaliculus is maintained stretched in a lateral direction so that the punctum and canaliculus are on a straight line. If this is not done, the dilator and subsequently the lacrimal cannula may strike against a fold of mucosa and produce a false passage if the pressure is continued. The dilator is then quickly exchanged for a loaded control three-ring dental syringe and gold curved cannula. The cannula is introduced vertically, rotated through 90°, slid along the canaliculus which is stretched into a straight line until the bony wall of the nose is felt through the medial wall of the lacrimal sac. It is then withdrawn a few millimeters and 1 to 2 cc. of sinografin is injected slowly. If patency exists, the patient very rapidly tastes the fluid and at this point static filming can be instituted. Occlusion below the bifurcation of the canaliculi may result in regurgitation through either the lower or upper punctum or both. Often it is worthwhile everting the upper lid, directing the patient to look downward and injecting the upper canaliculus. When there is regurgitation through the opposite canaliculus, it should be occluded with the punctum dilator or with finger pressure over the punctum in order to obtain good filling of the canaliculi and filling of all the area up to the point of complete or partial obstruction. The creases of the skin about the eye and the eyelashes should be wiped free of any spilled medium. The main hazard of the procedure is that of creating a false passage by faulty technique when inserting the cannula. However, the use of aqueous medium is much safer in that the medium is rapidly absorbed, whereas oily media will remain in the tissues for several years (Fig. 3, *A* and *B*).

The injection procedure can be done either in the supine or erect position. However, filming in the erect position using the Gianturco skull device and the effect of gravity is most convenient. When a single injection is made, roentgenograms are taken in the posteroanterior, Waters' (nose-chin), and lateral projections. If both sides are injected, 45° oblique roentgenograms are taken in addition, in order to prevent superimposition in the lateral projections. Stereoscopic roentgenograms, tomograms, and even magnification macrodacryocystograms[3] are also useful. Anatomically, the nasolacrimal canal passes obliquely downward dorsally and laterally and the plane of the nasolacrimal duct is parallel with the tabletop in the nose-chin position. (The orbitomeatal line should make an angle of 37° to 40° with the tabletop.) The infraorbital rim should be

* Allergan Pharmaceuticals, Santa Ana, California.

centered to the film. Thus, the passages are projected with minimal distortion and the petrous temporal bone is projected away from the orbit across the antrum. Delayed erect roentgenograms may be taken after 15–30 minutes if there is partial obstruction with dilatation of the nasolacrimal system. Normally the aqueous medium enters the nasal fossae immediately, leaving only a small fine coating on the passages. With partial obstruction there will be delayed emptying.

ROENTGEN ANATOMY OF THE LACRIMAL PASSAGES

The lacrimal passages extend from the lacrimal puncta at the nasal ends of the eyelid margins to the inferior opening of the nasolacrimal duct in the medial wall of the inferior meatus. The drainage passages are divided into superior and inferior canaliculi, the common canaliculus, the lacrimal sac, the nasolacrimal duct and the inferior orifice (Fig. 1).

All of these parts may be studied and visualized roentgenographically. A schematic representation of the anatomy, slightly modified from Campbell,[3] is shown in Figure 2. The canaliculi leave the lids, the upper slightly medial to the lower, extending medially in two directions and joining in the common canaliculus (sinus of Maier, or the ampulla of the canaliculi) to enter near the apex of the lacrimal sac. This opening is covered by flaps of mucosa called valves (the valve of Rosenmüller superiorly and the valve of Huschke inferiorly). The common canaliculus (sinus of Maier) is 1 to 3 mm. long and is situated on the lateral aspect near the apex of the lacrimal sac. It is visualized on both the anteroposterior and lateral roentgenograms with the canaliculi converging into it. It may be seen better roentgenographically when macroroentgenographic techniques are used.[3]

The lacrimal sac, which lies in the lacrimal fossa on the lateral aspect of the nasolacrimal bone, averages approximately 10 to 12 mm. in length and 1 to 2 mm. in width. It is normally not dilated. Its termination is marked by the constricting band of the split fascia of the orbicularis muscle, and it is also marked at this point by a mucosal fold called the valve of Krause. The actual junction of the neck of the sac with the nasolacrimal duct has been shown to lie well above the level of the bony rim of the orbit and, in fact, lies 5 to 7 mm. above the bony rim of the osseous nasolacrimal canal. On the frontal roentgenogram the normal lacrimal sac appears as an elongated shadow slightly wider at its

Fig. 1. Reconstruction of the nasolacrimal passages of an adult, aged 60 years. (Reproduced from Fig. 29, J. Parsons Schaeffer, *Am. J. Anat.*[16])

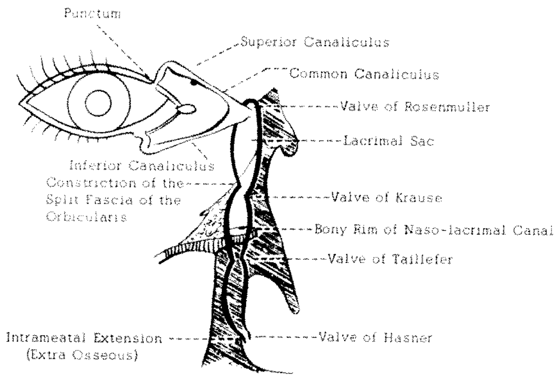

Fig. 2. Roentgenologic anatomy of the normal lacrimal system. (Reproduced with permission from *Brit. J. Radiol.*[3])

lateral aspect and normally shows no dilatation. Any visualized dilatation in the frontal view is pathologic. In the lateral view it normally bulges somewhat anteriorly, giving the sac an appearance of a "knife blade" (Fig. 4*A*). It is approximately 3 mm. in diameter in this view and can be up to three times wider than the measurement in the posteroanterior view (Fig. 4*B*). The absence of any dilatation in the lateral view and the absence of the "knife-blade" appearance are also pathologic, indicating that the lacrimal sac may be narrowed either from hypertonicity or actual fibrosis.

The nasolacrimal duct extends from the lacrimal sac to its inferior orifice in the medial wall of the inferior meatus of the nasal cavity. Campbell[3] has well demonstrated that the length of the nasolacrimal duct is greater than that which lies within the bony canal, which is a passage of only approximately 10 mm. (The osseous nasolacrimal canal is bordered laterally by the maxillary sinus from which it is separated by a thin bony wall. Medially, the bony canal passes along the lateral wall of the medial meatus.) In fact, there exists a membranous portion of the nasolacrimal duct which is within the orbit, not surrounded by bone, lying between the neck of the lacrimal sac and the superior bony foramen of the osseous portion of the nasolacrimal canal which adds an additional 5 to 7 mm. to the length of the duct. In addition, inferiorly there is a small intramembranous extension of the nasolacrimal duct, which is not surrounded by bone, prior to the opening into the orifice in the inferior meatus of the nasal cavity.[6] The nasolacrimal duct is cylindrical and somewhat flattened transversely; its total length therefore approximates 12 to 18 mm. and its diameter 2 mm. The termination of the lacrimal sac, marked by the constricting band of the split fascia of the

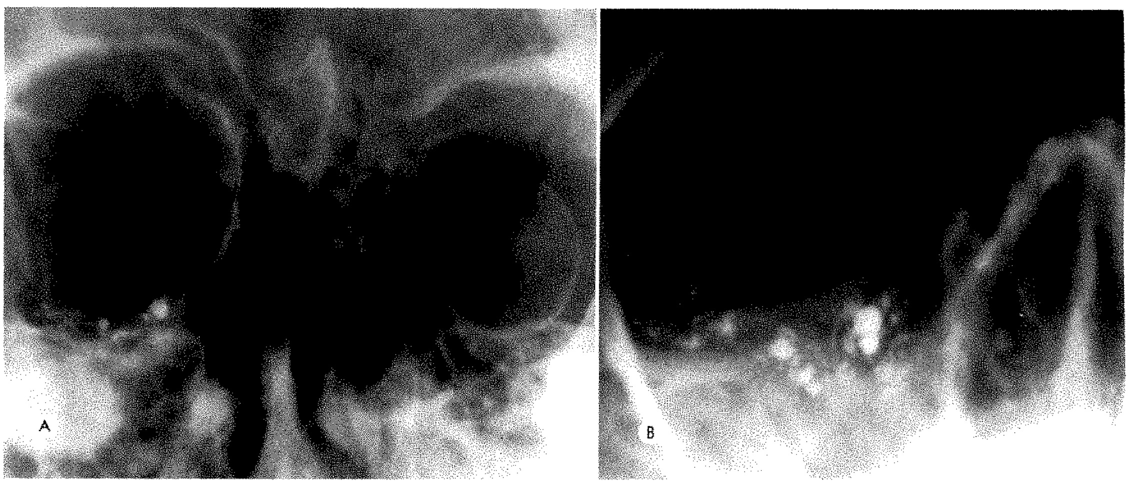

Fig. 3. (*A* and *B*) Extravasated oily opaque medium remaining in surrounding periorbital tissues for more than 3 years after the examination.

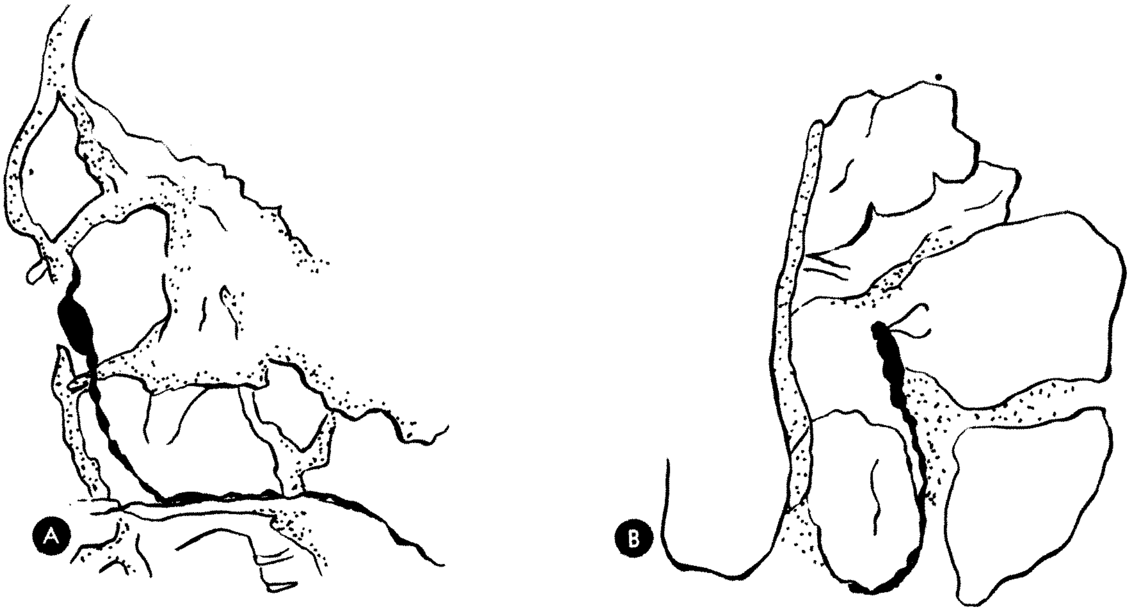

Fig. 4. (*A*) Lateral and (*B*) posteroanterior composite drawings from the series of normal roentgenograms.

orbicularis muscle, and also marked by the mucosal fold or the valve of Krause, constitutes the actual superior end of the nasolacrimal duct and is the narrowest part of the duct. The duct continues to widen as it progresses downward through the bony rim of the osseous canal. At a variable position within the canal, but usually in the middle of the intraosseous portion, there is a further constriction due to the mucosal valve of Taillefer. Finally, at its lower end, the nasolacrimal duct narrows sharply to form the valve of Hasner. The width of the nasolacrimal duct is fairly uniform, being as wide in the lateral view as it is in the posteroanterior view (Fig. 4, *A* and *B*) except for the abovementioned two constrictions, one at the superior junction with the lacrimal sac and one at the valve of Taillefer. The diameter of the normal lacrimal duct should not generally exceed 2 mm. and the duct assumes a more or less flexuose appearance because of mucosal valves.

Using aqueous media, the entire anatomic outline of the nasolacrimal passages as described above is rarely seen. Figure 4, *A* and *B* is a composite drawing from a series of normal roentgenograms. Using cineroentgenography[3,7] the normal nasolacrimal passages are seen to empty in 15 to 30 seconds so that the upper part of the passage is almost invariably emptied before static roentgenograms are taken. On the static roentgenograms a normal dacryocystogram presents as a smoothly irregular passageway, commencing at the inner canthus of the eye and ending below the inferior turbinate bone in the lateral wall of the nose. The general tendency is toward a tube of varying diameter. The walls may be likened to the esophagus in that they are approximated until separated and distended with the opaque medium. The flow of the medium is immediately apparent at the lower end of the passageway, flooding the nasal cavity and the nasopharynx (Fig. 5).

MATERIAL

A total of 17 cases (average age 50 years) were examined using sinografin to outline the nasolacrimal passages. The clinical indications were epiphora resulting from trauma, senile contractures of the nasolacrimal duct, and chronic infection. All of

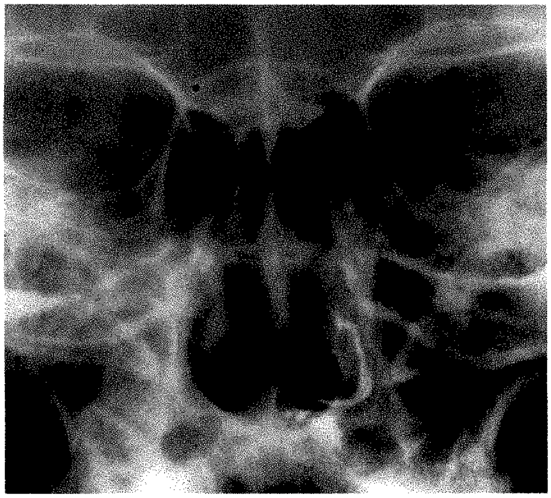

FIG. 5. Normal left dacryocystogram showing immediate "flooding" with opaque medium outlining the floor of the nasal cavity.

the patients examined had expressible mucus or pus from the lacrimal sac through the puncta, and most showed clinical evidence of chronic dacryocystitis.

Five of the 17 cases proved to have normal dacryocystograms. Of the 12 remaining, 1 (Fig. 3, *A* and *B*) showed a posttraumatic tear of the lacrimal sac with abnormal extravasation into the periorbital tissues. The abnormally extravasated oily medium (pantopaque) remained in the surrounding soft tissues for more than 3 years. Two of the patients demonstrated bilateral nasolacrimal sac neck obstructions which were complete.

Nine cases had unilateral obstruction of the nasolacrimal passages at varying points, extending from the neck of the sac through the inferior opening into the middle meatus (Fig. 6, *A* and *B*; 7, *A* and *B*; and 8, *A* and *B*). Of these 9 patients, only in two were the obstructions incomplete, showing delayed emptying, but all were associated with dilatation superior to the obstruction. Two of these 9 cases had previous surgery (dacryocystorhinostomies) prior to the roentgenographic study.

It is interesting to note that 4 of the patients had experienced severe maxillary trauma associated with car accidents in the past and 1 had a severe fist blow to the face, making a total of 5 patients who had obstruction following injury. Ten obstructed ducts were treated surgically (including the 2 patients with bilateral ob-

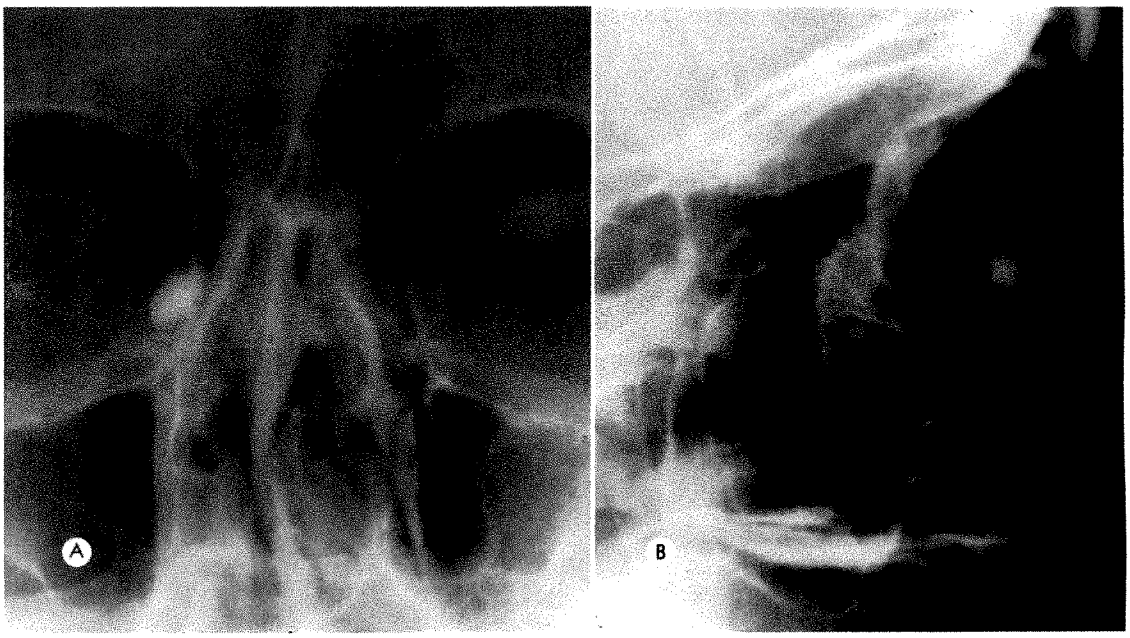

FIG. 6. (*A* and *B*) Right dacryocystograms showing obstruction distal to the distended lacrimal sac with narrowing at the level of the constricting band of the split fascia of the orbicularis muscle.

Fig. 7. (*A*) Posteroanterior and (*B*) lateral right dacryocystogram showing polycystic dilatation of the lacrimal sac.

structions). The operative procedure performed for relief of the obstruction was a dacryocystorhinostomy to effect the drainage of tears into the middle meatus of the nose by a short circuit made through the lacrimal bone and nasal mucosa.

Roentgenograms of the patients were taken postoperatively to obtain baseline films to show that the operative results were satisfactory and to identify the actual communication between the lacrimal sac and the newly created artificial orifice in the

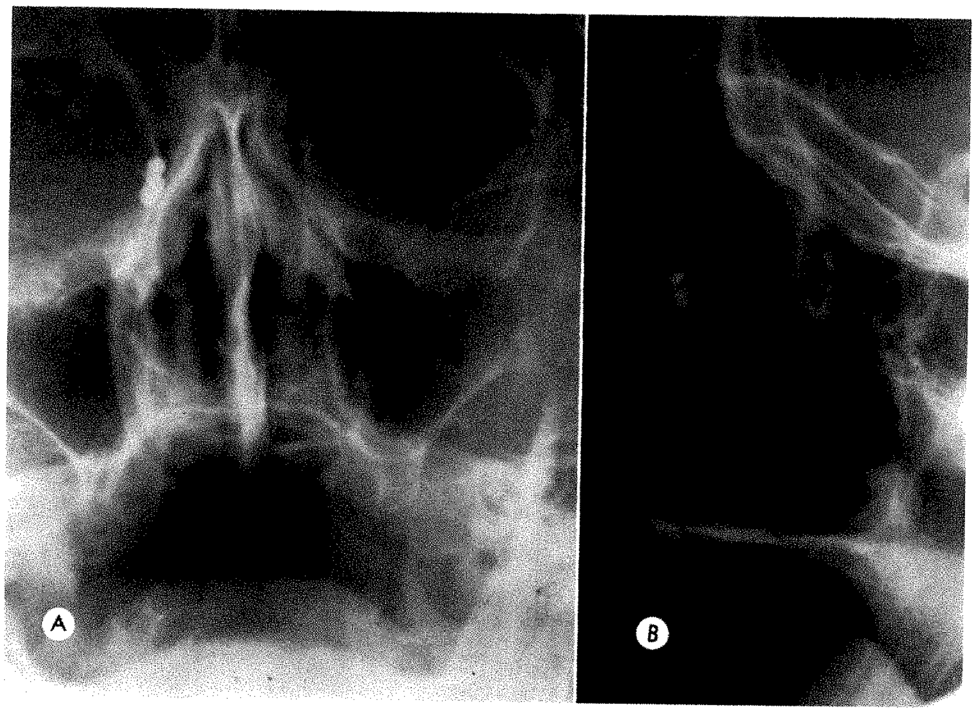

Fig. 8. (*A*) Posteroanterior and (*B*) lateral right dacryocystogram showing obstruction due to fibrosis.

area of the middle meatus of the nose. As a result of the immediate re-examination of the patients, 1 of the 7 patients was found to show postoperative obstruction and a postoperative failure. This patient was reoperated with satisfactory results. The 2 patients who had unsuccessful dacryocystorhinostomies at other institutions and who had roentgenographic demonstrable obstructions were also reoperated, with the postoperative examination showing again satisfactory canalization between the lacrimal sac and the middle meatus.

DISCUSSION

Epiphora, or weeping, with the spilling over of the tears from the conjunctival sac onto the cheeks is due to either excessive lacrimation or secretion of tears so that the lacrimal passages cannot adequately drain them away; or inadequacy or blocking of the lacrimal passages so that they cannot accommodate the normal secretion of tears which then spill onto the cheek, *i.e.*, obstructive epiphora.

Dacryocystography is valuable in the investigation of obstructive epiphora and may demonstrate the four main causes of the obstruction, *i.e.*, the puncta may be congenitally displaced or abnormal so that tears cannot enter them; the lacrimal passages may be blocked at some point by inflammation, neoplasm, trauma, atresia or fibrosis; the nose may be obstructed; and finally the passageways, although permeable, may be functionally inefficient. As the result of the roentgenographic investigation one should be able to determine the level of obstruction to the flow of tears and the degree of obstruction. Finally, if there is persistent tearing for reasons other than nasolacrimal obstruction, the dacryocystogram will reveal patency and will negate any further surgical approach and avert repeated probings.

The indications of abnormality[3] are: regurgitation through the opposite or same punctum during the injection; retention of the opaque medium in the canaliculi; the absence of flow of the opaque medium into the nasal cavity in all projections; flow into the nose but retention of the medium in the sac and duct with an increase in the over-all width of the sac or duct; variation in the caliber of the system, *i.e.*, more than would result from the mucosal folds which exist at various levels and the retention of the opaque medium above the constriction; and retention of the opaque medium throughout the duct over the period of time required for both the posteroanterior and lateral roentgenograms to be taken.

The level of an incomplete obstruction can be confirmed by further roentgenograms taken 15 minutes or more after the injection when the contrast medium is often still retained above the obstruction. This is very worthwhile in doubtful cases. The absence of contrast medium after this interval, however, is no proof that a partial obstruction still does not exist. The lower canaliculus suffers more frequently than the upper from inflammation of the medial canthus of the eye and is more important for drainage of tears. Occlusion of the upper canaliculus is of little consequence and does not cause epiphora when the lower canaliculus is patent.

Among the roentgenographic findings which should influence the management of chronic obstructive dacryocystitis one must also note the condition of surrounding paranasal sinuses; the position of the nasal septum; the amount of hypertrophy of the nasal turbinates; the presence of osteomyelitis in the surrounding bony structures; the condition of the orbital and nasal bones following trauma where fracture might be present; and, finally, the presence of tumors of bone or soft tissue in the vicinity of the nasolacrimal passages.

The presurgical value of dacryocystography is of inestimable value, not only to demonstrate the anatomic block, but also to demonstrate whether or not the sac is atonic and markedly stretched or shrunken and stenosed. The large atonic sac usually responds well to dacryocystorhinostomy. On the other hand, a shrunken sac presents an obstacle to the surgeon employing the

classical forms of dacryocystorhinostomy, and in such cases it is wiser to employ one of the techniques utilizing intubation of the system or even excision of the sac. In addition, dacryocystography can also demonstrate preoperatively whether or not there are fistulae or diverticula present. Postsurgically, the postoperative roentgenographic studies should show the possible causes of persistent discharge; for example, a lacrimal sac diverticulum not noted prior to surgery, postoperative fistulization, and secondary closure of the dacryocystorhinostomy opening. In addition, if a dacryocystectomy has been performed and there are residual sacs or infected pockets, these can be postoperatively identified.

SUMMARY

Sinografin is an excellent aqueous medium for dacryocystography for the reasons described, *i.e.*, safe, nontoxic and nonirritating and readily absorbed if it escapes into the surrounding soft tissues.

Routine use of roentgenography of the lacrimal passages is recommended in all cases of epiphora. The only contraindication is an acute infectious process of the eye or surrounding periorbital tissues.

Although the nasolacrimal system may exhibit patency by ordinary irrigation, impaired drainage function can be demonstrated by the dacryocystogram. This type of functional block may be an indication for dacryocystorhinostomy.

When patency of the lacrimal passages cannot be demonstrated by routine irrigation, the preoperative use of dacryocystography is indicated to show the character of the structures adjacent to the passages, the position and extent of the stenosis, and the size and tonus of the sac and ducts. Following operative procedures, the dacryocystogram is useful in evaluating the results of surgery.

Further study of the normal and abnormal physiology of the lacrimal system is indicated using aqueous media and cinefluorographic studies.

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RECOGNITION AND MANAGEMENT OF FRACTURES OF THE ORBIT*

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IN THESE days of highway violence, there is an increasing incidence of severe facial injuries. Many of these involve the orbit. Since the radiologist is often one of the first physicians to see these victims, he must know the clinical findings in various fractures of the orbit. By correlating the physical findings with the results of a personally supervised roentgen examination, a correct diagnosis can usually be made. The radiologist can then direct the therapy into the proper channels.

The purpose of this paper is to acquaint the radiologist with the clinical syndromes, the roentgen findings, and the treatment of the various orbital fractures.

The fractures of the orbit may be classified into:

- I. Fracture of the floor:
  - A. External—involving the infraorbital rim.
  - B. Internal—not involving the infraorbital rim.
- II. Fracture of the medial wall.
- III. Fracture of the roof and lateral wall.
- IV. Fracture of the optic canal.

This classification reflects their relative frequency; however, it is not unusual to have a patient sustain more than one of these fractures from a single traumatic episode, and perhaps a fifth category named "mixed fractures" should be added.

In the roentgen examination, the views in which the roentgenograms are made will vary from patient to patient depending on the clinical picture. However, in general, the roentgen examination should include:

1. A Waters view, or multiple modifications of the Waters view, for the floors of the orbits and the maxillary sinuses.
2. A Caldwell view for the medial walls, roofs and lateral walls of the orbits and the ethmoid sinuses.
3. A lateral view for the roof and floor of the orbit.
4. Oblique views for the lateral walls of the orbits and the optic canals, and, if necessary,
5. Laminagrams in the straight anteroposterior and/or "personalized" Waters projection.

If possible, all these roentgenograms should be made in the erect position to demonstrate air-fluid levels in the maxillary sinuses and orbital emphysema.

I. FRACTURE OF THE FLOOR OF THE ORBIT

In the past 3 years, the most common fracture that we have seen in the facial bones (excluding the nose) has been a fracture of the floor of the orbit (Fig. 1).[2,3,4] It is usually produced by a direct blow,

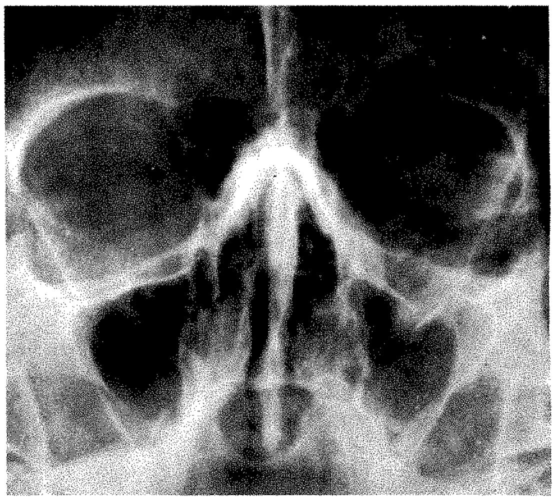

FIG. 1. Fracture of the floor of the left orbit with orbital emphysema and clouding of the left antrum.

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either to the malar eminence or to the eye itself. Because of the nature of the orbital contents, direct pressure on the fluid-filled globe will be transmitted equally in all directions. The floor is the thinnest portion of the orbit and hence the first part to fracture. Since the normal globe is supported by the bony orbital floor and the hammock-like suspensory ligament of Lockwood, fracture of the floor and rupture of the ligament allow depression of the eyeball. Incoordination of the eyes and diplopia may result. The detection of very subtle changes in ocular coordination can be extremely difficult. For this reason, an ophthalmologist should examine these patients soon after injury and then at frequent and regular intervals.

Common physical findings with a fracture of the floor of the orbit are:

1. Periorbital edema, ecchymosis and subconjunctival hemorrhage.
2. Numbness of the cheek from injury to the infraorbital branch of the fifth nerve which lies in the floor of the orbit.
3. Transient proptosis from retrobulbar hemorrhage.
4. Deviation of the axis of the globe so that the eye looks up (hypertropia); and rarely
5. Emphysema of the eyelids due to the escape of air from the maxillary sinus.

When the floor of the orbit is fractured, the roentgen examination will usually show:

1. Opacification of the maxillary sinus by hemorrhage.
2. A fracture of the floor of the orbit with varying degrees of depression of the fragments.
3. Orbital emphysema.

When a fracture of the floor of the orbit has been demonstrated, and the patient has diplopia, surgical correction is usually necessary. In some cases, the roentgen findings are equivocal and a definite fracture is not seen. Even in these patients, if ocular incoordination is present, surgical

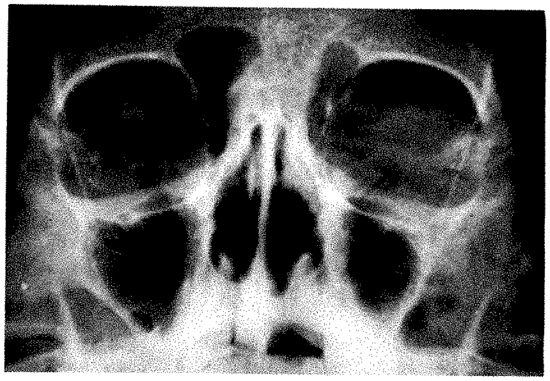

Fig. 2. Fracture of the medial wall of the left orbit with clouding of the left ethmoid sinus and orbital emphysema. Note that the orbital floor is intact and the left antrum is clear.

intervention should be considered. The treatment usually consists of exploration of the antrum through a Caldwell-Luc type of approach with elevation of the orbital floor either by packing or by means of an inflatable balloon. If the patient is under local anesthesia, the correction of the diplopia may be used as an end-point in determining a satisfactory reduction. This reduction should be done early to prevent mal-union and permanent enophthalmos.

II. FRACTURE OF THE MEDIAL WALL OF THE ORBIT

Fracture of the medial wall of the orbit (Fig. 2) is caused by a slightly different mechanism than that producing fracture of the floor, although the two are frequently seen together (Fig. 3). There may be either direct trauma to the ethmoid region itself, or, if the globe is struck, it is by a hooking rather than a jabbing blow.

Physical examination of a patient with a fracture of the medial wall of the orbit usually shows:

1. Periorbital edema and ecchymosis with or without subconjunctival hemorrhage.
2. Absence of numbness of the cheek.
3. Absence of eye signs, unless the floor is also fractured.

The roentgen examination of the patient with a fracture of the medial wall of the orbit may show:

Fig. 3. Fractures of the medial walls of both orbits and floor of the left orbit. The air-fluid level in the right antrum suggests fracture of the orbital floor on this side also.

1. A fracture line (which may be difficult to demonstrate).
2. Unilateral clouding of the ethmoid sinus.
3. Orbital emphysema (more common than in fracture of the floor).
4. Absence of hemorrhage in the antrum.

Occasionally orbital emphysema may be demonstrated only by a roentgenogram made in the erect posture, during forced expiration with the patient's mouth closed and his nose clamped.

Supportive measures plus antibiotics to prevent infection are usually adequate treatment for fractures of the medial wall.

III. Fracture of the Roof and Lateral Wall of the Orbit

Isolated fractures of the anterior portion of the roof of the orbit (Fig. 4) require a highly localized, very severe and hence quite unusual insult. If they do not involve the supraorbital rim but are limited to the floor of the anterior cranial fossa, their roentgen demonstration may be very difficult. More commonly, fractures of the roof and lateral wall are part of a multiple fracture complex involving the calvarium as well as the face (Fig. 5). Because of the severe forces involved brain damage may be present, and these patients should be treated jointly by the neurosurgeon, the maxillofacial surgeon, and the ophthalmologist.

IV. Fracture of the Optic Canal

Fracture of the optic canal (Fig. 6) usually follows a blunt, forceful blow to the forehead, although occasionally the initial insult may have seemed trivial and the patient will recall only having been "dazed" briefly. Soon after the accident, or immediately upon recovering consciousness, the patient may state that he is partially or totally blind in one eye.

In some patients presenting this clinical picture, no fracture can be shown roentgenologically. Damage to the optic nerve

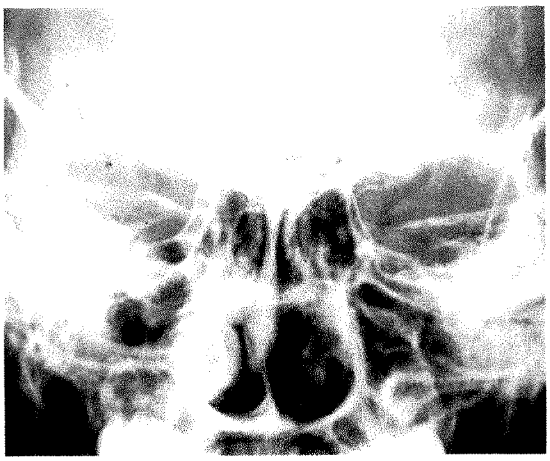

Fig. 4. Isolated fracture with elevation of the right supraorbital rim.

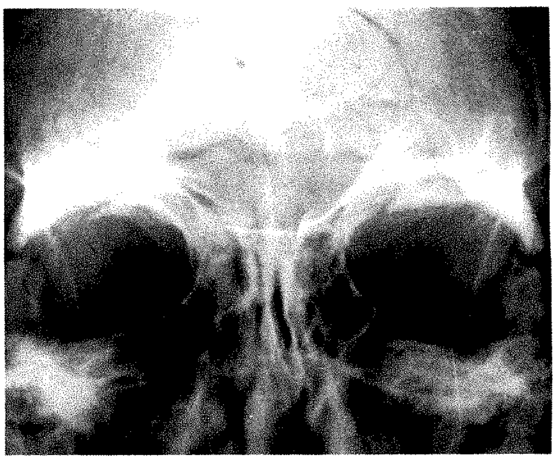

Fig. 5. Fractures of calvarium, roofs and lateral walls of both orbits.

in these cases may be due to ischemia, compression of the nerve by hemorrhage, or a fracture that has reduced itself.

Rarely, a patient whose vision was unaffected originally may show progressive visual deterioration weeks and even months after the injury. This may be due to fibrosis and callus formation causing increasing pressure on the optic nerve.

When a fracture of the optic canal produces a deficit in vision, immediate decompression of the optic nerve is required to restore sight.[1] However, because of associated head injuries, many of these patients are not able to undergo this formidable procedure.

SUMMARY

1. Fractures of the bony orbit present definite patterns.
2. They may be of no clinical significance or may lead to incapacitating ocular disability and even blindness.
3. Diagnosis of these fractures may be impossible without a knowledge of the clinical findings and correlation of these findings with the roentgen signs.
4. Treatment of these fractures demands the combined skills of medical specialists in widely-separated fields.
5. The recognition of these fractures and a knowledge of their treatment will allow the radiologist to contribute greatly to the patient's management.

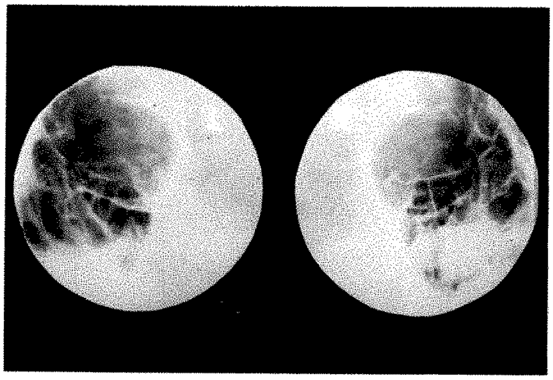

Fig. 6. Fracture with elevation of roof of left optic canal.

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SOFT TISSUE ROENTGENOGRAPHY OF THYROID NODULES*

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CARCINOMA of the thyroid gland, in most instances, eludes definitive preoperative diagnosis. Diagnostic roentgenology has contributed relatively little to the evaluation of a thyroid nodule for malignancy.

As an aid in the differentiation of benign and malignant thyroid disease, several roentgenologic techniques have been employed. Laminagraphic examination of the neck after injection of gas into the soft tissues around the thyroid gland has been performed by Rozenshtraukh and Ponomarev,[12] as well as by other European investigators. Although this technique succeeds in demonstrating the extent and configuration of thyroid tissue, it has no definitive value in the diagnosis of malignancy. The applications of thyroid arteriography have been described recently by Djindjian *et al.*[2] Ritvo[11] has attempted to correlate tracheal configuration with carcinoma of the thyroid gland. A later study by Schein *et al.*[13] showed this method to be unreliable and frequently misleading. Thyroid enlargement as manifested in the plain roentgenogram of the neck and in the barium esophagogram has recently been discussed by Kreel[8] and his associates.[9] They described no features by which benign or malignant thyroid diseases can be distinguished reliably.

PSAMMOMA BODIES AND THYROID CANCERS

Histologic examination of thyroid carcinomas frequently reveals characteristic spherical calcifications called calcospherites or psammoma bodies. These are rounded, basophilic, concentric, usually lamellated bodies varying in diameter from 10 to 100 microns. Although they are most common in papillary carcinomas, they may be present in all types of epithelial neoplasms of the thyroid gland. Klinck and Winship,[7] in a histologic study, examined thyroid tissue from 2,626 patients; among the 470 carcinomas in this group, psammoma bodies were found in 48 per cent. Distributed by histologic type, these calcifications were seen in 61 per cent of papillary carcinomas, 26 per cent of follicular carcinomas, and 13 per cent of undifferentiated malignancies. In 21 per cent, the calcification was not present in the primary tumor itself, but in the adjacent normal gland. The calcifications appeared to be more common in childhood cancer than in that of the adult. Psammoma bodies appeared in 29 per cent of metastatic thyroid lesions. Of most importance was the observation of psammoma bodies in only one noncancerous thyroid gland.

The roentgenologist is familiar with the roentgen appearance of the calcified psammoma body. These bodies are found in many tumors and at different sites.[1] They may be seen in cystadenoma or cystadenocarcinoma of the ovary, meningioma, renal cell carcinoma, some gastrointestinal carcinomas, and in bronchiolar cell carcinoma of the lung. Psammoma bodies in thyroid carcinoma, therefore, are of interest to the radiologist as well as to the pathologist. When they are sufficiently numerous or conglomerate, these bodies are visible roentgenologically.

ROENTGENOLOGIC APPEARANCE OF THYROID CALCIFICATION

Evidence of calcification within the thyroid gland is frequently seen in ordinary roentgenograms of the neck or chest. Segal

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et al.,[14] agreeing with Holtz and Powers,[6] proposed criteria for roentgenographic differentiation of the calcium deposits that are associated with benign and malignant disease. The roentgenograms must show the bodies to be poorly marginated, hazy, not densely calcific, about equal in size, and usually grouped in streaks or in a nebular formation within a well-limited area that does not have a calcific rim (Fig. 1*A*). Calcifications of a benign nature are usually dense, sharply marginated, and of variable size and distribution (Fig. 1*B*). The authors expressed the belief that a clear differentiation between these two groups of calcifications can be made from plain roentgenograms of the neck. Similar conclusions were reached by Fournier and Jouve-Fournier.[4] The presence of psammoma bodies within the gland was considered as diagnostic of carcinoma. Psammomatous calcification was noted by Holtz and Powers[6] in roentgenograms of the neck or chest of 3 patients. Later histologic study revealed papillary carcinoma with psammoma bodies in these glands. Segal *et al.*[14] obtained soft tissue roentgenograms of the neck of 29 patients with thyroid masses before thyroidectomy. In 3 patients psammomatous calcification was demonstrated roentgenographically and psammoma bodies were present histologically. The carcinomas in these patients were also of the papillary variety. No false-positive results were obtained.

Gerard-Marchant *et al.*[5] performed preoperative roentgen examinations on 44 patients with thyroid masses, employing oblique and lateral projections of the neck on non-screen film. These roentgenologic results were subsequently correlated with the results of the histologic examination, as well as with the roentgen appearance of the excised specimen. In the 10 carcinomas in their series, evidence of psammomatous calcification was seen on roentgenograms of the neck in 5 instances, but was demonstrated histologically in only 4 of these.

A retrospective study by Erazo and Wahner[3] of neck roentgenograms in 28 patients with benign nodular goiter and 47

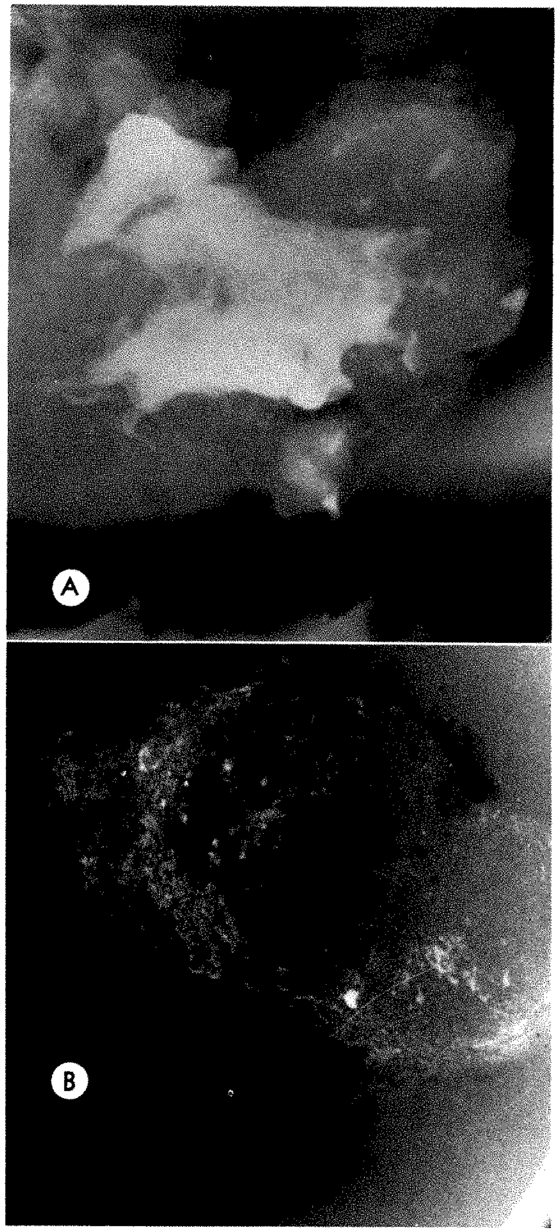

Fig. 1. (*A*) Dense, amorphous plaques of coarse calcification in a benign nodular goiter. (*B*) Typical psammomatous calcification in a papillary adenocarcinoma. (Reproduced with permission of *Investigative Radiology*.[10])

patients with thyroid carcinoma showed calcification in 73 per cent of the benign neoplasms. These deposits were all of the coarse amorphous type, except in one instance in which psammomatous calcification was seen. Of their patients with thyroid carcinoma, typical benign calcifica-

tions were seen in 35 per cent and characteristic psammomatous calcifications in 6 per cent.

CURRENT INVESTIGATION

In none of the previously cited investigations was soft tissue roentgenography performed with a technique incorporating principles designed to provide optimal contrast and detail. These principles, as used in mammography, include: (a) low kilovoltage and high milliamperage; (b) no filtration; (c) short object-to-film distance; (d) fine grain, non-screen, industrial type film; and (4) manual processing.

The results of previous studies would suggest that further study of the correlation of calcification and thyroid disease is indicated. A reliable and reproducible technique for the *in vivo* demonstration of psammoma bodies would be of considerable value in the management of patients with nodular thyroid enlargement. A technique was devised that closely approximated that used in mammography. The current study was undertaken to determine if the application of these fundamentals of soft tissue roentgenography would provide sufficient detail to clearly differentiate between benign and malignant calcification.

METHODS AND MATERIALS

Roentgenograms of the neck were obtained in all patients with thyroid nodules admitted for surgery at the University of California Medical Center between May, 1965 and September, 1966. Most patients with known, diffuse hyperplastic goiter were excluded from the study, as the incidence of carcinoma is only 0.15 per cent in this group.[15] Thus, a total of 100 patients were studied in the preoperative period. An additional 14 out-patients were examined in whom surgical proof is not yet available. In all 114, clinical examination of the neck was performed by one of us (F.R.M.) before roentgenography.

Small lead markers overlying the clavicular insertion of the sternocleidomastoid muscle identified the right and left sides. 69 instances, routine lateral and obliq soft tissue roentgenograms of the neck we first obtained on Du Pont Cronex I film wi screen cassettes. The exposure factors we 56 kv., 300 ma., one-tenth second a 72 inches target-to-film distance.

After this roentgenography, with equi ment routinely employed for mammo raphy, a soft tissue examination of t neck was done. After considerable e perimentation with technical factors a patient positioning, the following pr cedure was adopted. The patient is plac prone on the roentgenographic table wi the neck flexed over the edge of the tal (Fig. 2). A small sandbag is inserted conform to the curvature of the neck a a malleable plastic 5 × 7 inch cassett is placed lengthwise upon the sandbag. T head is then allowed to drop over the ta edge to its most dependent position, a the chin is turned laterally. The ante lateral aspect of the neck is thus in cont with the film cassette and one of the th roid lobes is brought into relief. The tu with its extension cone is then angula 15° toward the patient and 10° cauda

* Anscoflex. General Aniline and Film Corporation.

Fig. 2. Position of patient, cassette, and tube oblique exposure. The weight of the patient's h hanging over the table edge keeps the sand and cassette in place. The anterolateral as of the neck is in contact with the film cassett

in order to project the shoulders downward. In this position, the oblique roentgenogram is obtained. The opposite oblique roentgenogram is made in a similar manner. Next, the patient is rotated into a steep oblique position with the desired side downward. A single, slightly off-lateral projection is then obtained with the tube angled 5° toward the patient and 5° caudally. The technical factors used for the oblique exposure are: 56 kv., 300 ma., 3 seconds and 26 inches target-to-film distance. For the lateral roentgenogram 48 kv., 300 ma., 3 seconds and 28 inches target-to-film distance are used. No filtration is added.

It must be emphasized that the above technique was most frequently applied to the average patient. Those with long, slender necks generally required less exposure, resulting in roentgenograms of excellent quality. Short, thick-necked and elderly patients posed a major technical problem for which tube distance, angulation, and exposure factors had to be individually adjusted.

The exposure factors listed above were those required by the tube that was used throughout most of the study. When a new beryllium window tube was employed during the latter part of the study, reduction of exposure time by 50 to 60 per cent was possible in the average patient.

Many non-screen and industrial films were tested for contrast and sharpness of detail by roentgenography of specimens known to contain psammoma bodies. Kodak M and AA-film provided superior image resolution. On further testing, the latitude of these films was determined to be sufficiently complementary to allow both to be used in the same cassette. This double-loading technique thus produced 6 roentgenograms of the neck in 3 positions, using only 3 exposures. Initially, automatic processing was used, but the results were inferior to those obtained by manual development of the industrial film for 8 minutes.

Roentgenograms of 81 specimens were obtained, 4 exposures being made of each specimen, for 2 of which the tissue was placed in a water phantom. The identity of right and left lobes and upper and lower poles was preserved whenever possible. All roentgenograms were examined at least twice with a hand lens under intensified illumination.

RESULTS AND DISCUSSION

The findings in 16 patients with thyroid carcinoma are presented in Table I. In only 3 patients, all with papillary adenocarcinoma, could very faint psammomatous calcification be recognized on soft tissue roentgenograms of the neck (Fig. 3, *A-C*; 4, *A* and *B*; and 5, *A* and *B*), although histologically, psammoma bodies were present in 10 patients. In 1 of these 3 patients, the psammoma bodies were identified on routine roentgenograms of the neck, adjacent to the hyoid bone anteriorly. At surgery, papillary carcinoma was discovered in a thyroglossal duct cyst in this region. An additional, densely calcified nodule was present in the left lobe of the thyroid gland which, at a second operation, proved to contain a central focus of papillary carcinoma. In another patient, coarse calcific deposits were combined with calcification in a psammomatous pattern. In no instance was psammomatous calcification seen in cervical lymph nodes that later were shown to contain metastatic thyroid carcinoma. In 1 patient, roentgenograms of a large metastatic deposit in the anterior chest wall were obtained, but calcification was not demonstrated in this mass.

In roentgenograms of specimens of glands containing carcinoma, coarse calcification and combined coarse and psammomatous calcifications were present more often than were psammoma bodies alone. Coarse calcification was present histologically at some distance from the carcinoma in all instances but one. In this specimen, a papillary carcinoma containing psammoma bodies was described within the center of a well calcified adenoma. That the coarse deposits of calcium seen on

Table I

CALCIFICATION IN THYROID CARCINOMAS

	All Carcinomas	Final Histologic Diagnosis: Papillary Carcinoma	Follicular Carcinoma	Mixed Papillary and Follicular Carcinoma	Medullary Carcinoma
No. of Patients:	16	10	3	2	1
Calcification in Roentgenogram of Neck					
None	9	5	1	2	1
Coarse	4	2	2	0	0
Psammomatous	2	2	0	0	0
Combined	1	1	0	0	0
*Calcification in Roentgenogram of Specimen**					
None	3	1	0	1	1
Coarse	6	3	3	0	0
Psammomatous	3	2	0	1	0
Combined	3	3	0	0	0
Calcification on Histologic Examination of Specimen					
None	3	1	1	0	1
Amorphous	3	1	2	0	0
Psammomatous	7	5	0	2	0
Combined	3	3	0	0	0

* Roentgenogram of specimen not obtained in 1 patient with papillary carcinoma.

roentgenograms of some of the specimens were either not included in histologic sections, or not described by the pathologist, is recognized. A more detailed roentgenologic and histologic correlation of calcification in 102 thyroidectomy specimens has been reported elsewhere.[10]

Roentgenograms of the neck of 84 patients with nonmalignant disease (Table II) disclosed coarse, dense calcium deposits in 23 per cent. These were most frequent in patients with nodular goiter. Commonly, in these instances, calcification not seen in preoperative roentgenograms was revealed in the roentgenograms of the specimens. In some of these, the technique of the preoperative examination had been inadequate for demonstration of the calcification. In others, the calcific foci may have been either very small or in a substernal location.

Although, occasionally, psammomatous calcification in thyroid carcinoma may be quite dense and easily recognizable on plain roentgenograms of the neck without special roentgenographic technique, in most instances this calcification is faint and ill-defined. Roentgenograms obtained with the technique applied in this study were compared with routine studies of the soft tissues of the neck. The results indicated that the dense, as well as the faint, areas of calcium could be much better defined by employing the former technique (Fig. 3, *A-C*). Prolonged exposure times ranging from 1 to 3 seconds inevitably allowed some motion from vascular pulsation, even in the most cooperative patients. The technical

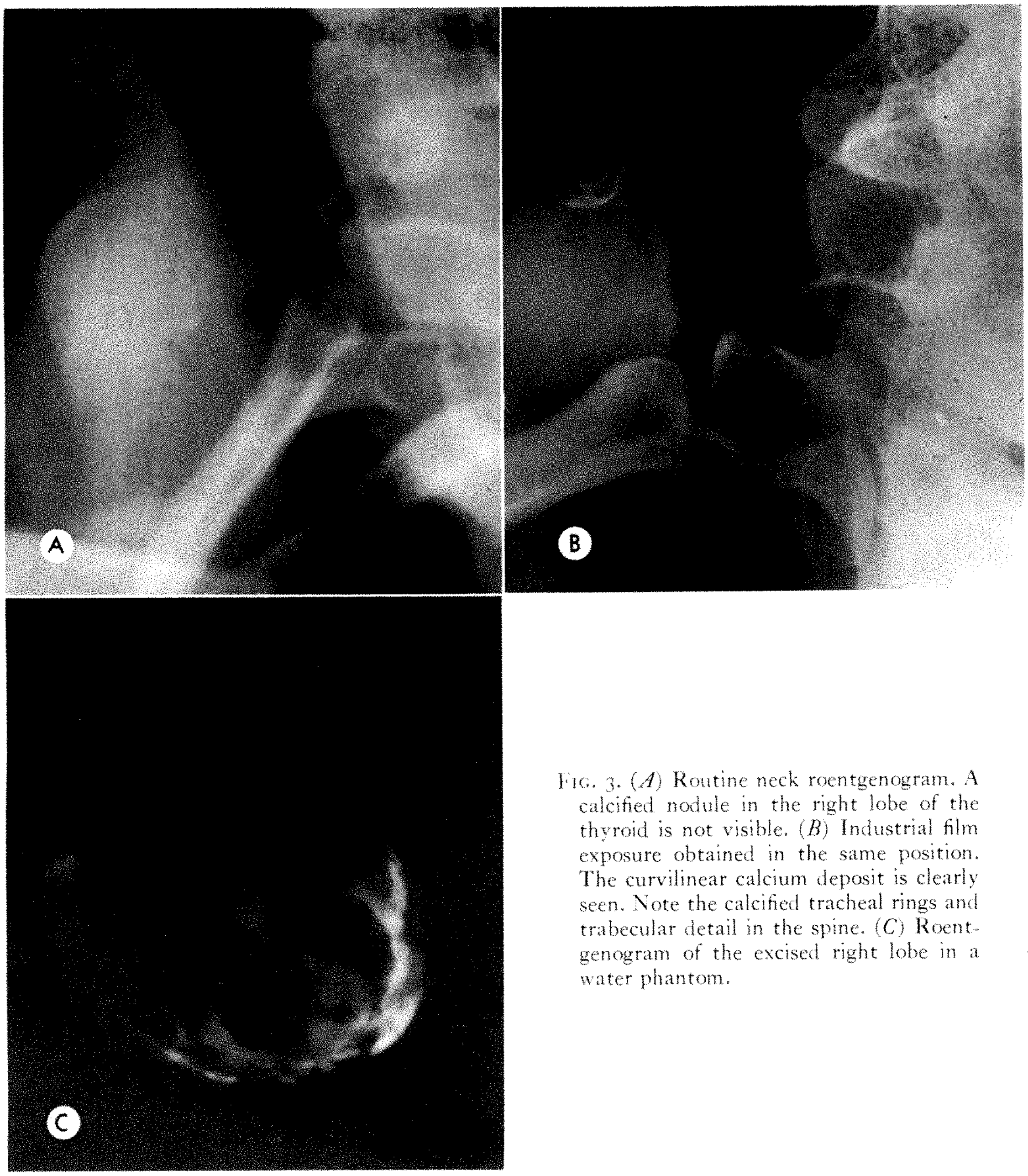

Fig. 3. (*A*) Routine neck roentgenogram. A calcified nodule in the right lobe of the thyroid is not visible. (*B*) Industrial film exposure obtained in the same position. The curvilinear calcium deposit is clearly seen. Note the calcified tracheal rings and trabecular detail in the spine. (*C*) Roentgenogram of the excised right lobe in a water phantom.

quality of the roentgenograms obtained, however, was superior to the routine exposures of the neck in nearly every instance. The greatly decreased object-to-film distance and the weight of the patient's dependent head, tending to immobilize the neck, probably more than compensated for any motion inherent in the longer exposure time.

The calcified cartilaginous structure of the larynx and trachea could be extremely well defined in most of the patients. Although no abnormality of these structures was recognized, the technique may prove to be of value in the assessment of traumatic and destructive processes in these areas.

Histologically, psammoma bodies can

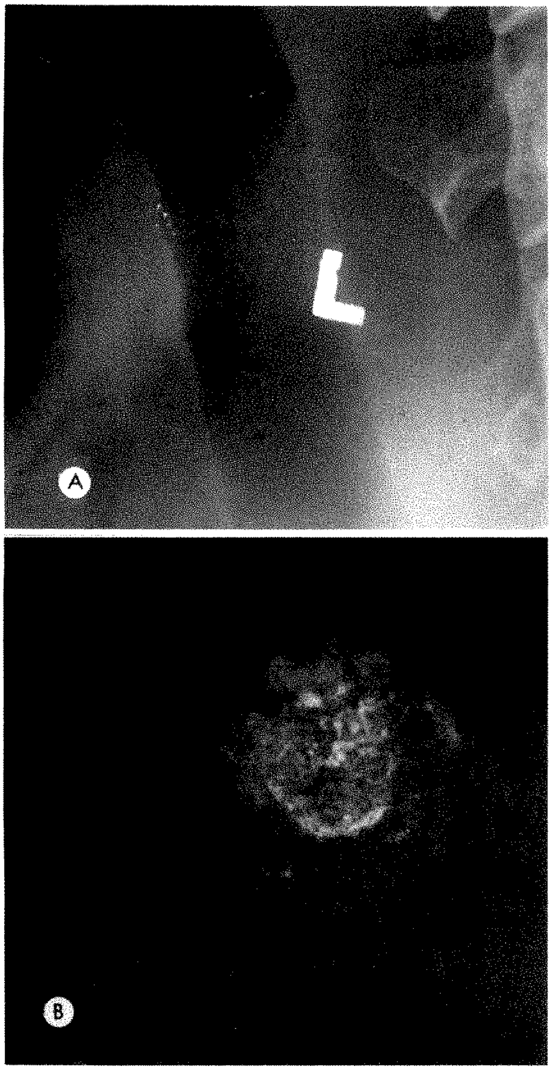

Fig. 4. (*A*) Industrial film roentgenogram showing very faint calcium deposits superimposed on the tracheal air column. The calcification is psammomatous in nature. (*B*) Roentgenogram of the surgical specimen: a papillary adenocarcinoma. A psammomatous pattern is evident.

be expected in approximately 50 per cent of thyroid cancers. Most often, they are of insufficient density and number to allow roentgenographic identification *in vivo* despite attention to technical details of soft tissue roentgenography. Sufficiently numerous or conglomerate psammoma bodies may sometimes be identified on routine roentgenograms of the neck or chest, without recourse to the soft tissue technique applied in this study. When noncalcified carcinomas and those containing too few psammoma bodies to be seen even on technically optimal roentgenograms are eliminated, the remaining carcinomas containing psammoma bodies potentially demonstrable only with the technique described here, are disappointingly few.

This method of examination could probably be employed with success in those instances in which routine roentgenograms

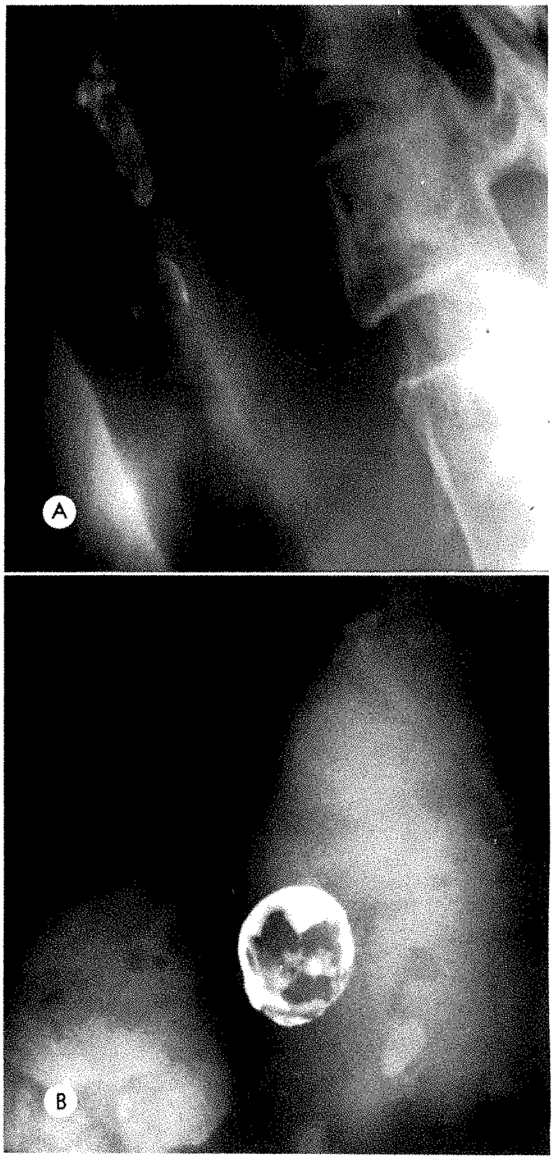

Fig. 5. (*A*) A well calcified nodule seen with industrial film technique. (*B*) Roentgenogram of the specimen: a benign adenoma.

TABLE II

CALCIFICATION IN BENIGN THYROID DISEASE

	Final Histologic Diagnosis				
	Follicular Adenoma	Hashimoto's Thyroiditis	Nodular Goiter	Diffuse Hyperplasia	Total
No. of Patients:	28	11	35	10	84
Calcification in Roentgenogram of Neck					
Coarse	3	1	15	0	19
Calcification in Roentgenogram of Specimen					
Amorphous	8	2	23	2	35
Calcification on Histologic Examination of Specimen					
Amorphous	6	1	15	0	22

of the neck suggest the presence of hazy thyroid calcification. Soft tissue roentgenography to show that this calcification is of a psammomatous nature will, with few exceptions, establish the presence of carcinoma within the gland.

SUMMARY

Calcified psammoma bodies are seen histologically in 50 per cent of thyroid carcinomas, but extremely rarely in benign disease. When sufficiently numerous or aggregate, these cast a discernible roentgen shadow, usually appearing as hazy, ill-defined areas of only slight opacity. Their recognition will allow a preoperative roentgen diagnosis of carcinoma to be made. Coarse, dense calcific deposits in the thyroid are frequently recognized roentgenographically. These are nonspecific in nature and bear no predictable relationship to malignancy.

Soft tissue roentgenograms of the neck in 100 preoperative patients with thyroid nodules revealed abnormal calcium deposits in 26 per cent. In only 3 patients in whom calcium was shown on roentgenograms of the neck was a psammomatous pattern demonstrated. All 3 of these patients had papillary adenocarcinoma. Histologically, psammoma bodies were found in specimens of 10 of 16 patients with thyroid carcinoma.

The method of soft tissue roentgenography of the neck, as described here, produces roentgenograms of excellent technical quality. There is little, however, to recommend its routine use in the evaluation of thyroid nodules. This method of study may well be useful when clinical findings strongly indicate that a nodule is malignant. It may be further applied as a supplement to routine roentgen examination in which deposits of calcification are considered suspicious. Psammomatous calcification in metastatic deposits of thyroid carcinoma has not been demonstrated roentgenographically.

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OBSTRUCTIVE CARDIOMYOPATHY*

CINEANGIOCARDIOGRAPHIC STUDY OF 50 CASES

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PARIS, FRANCE

THE clinical, electrocardiographic and hemodynamic signs of obstructive cardiomyopathy are quite well known. Recent publications, however, have cast some doubt as to the exact site of the left ventricular obstruction.

The purpose of this paper is to describe the various morphologic anomalies of the 4 heart chambers, and to attempt an accurate localization of the site of obstruction.

MATERIAL

This study concerns 50 cases of obstructive cardiomyopathy, the diagnosis of which was based on the clinical, electrocardiographic and hemodynamic signs previously reported.[2,3,7,17,20,25] Fourteen of them have undergone surgery and two others have been examined post mortem. A left intraventricular pressure gradient was found in 40 cases under basal conditions (average value 77 mm. Hg). In 6 cases, the left ventricular pressure gradient was demonstrated only after isoproterenol infusion (average value 72 mm. Hg). In the 4 cases in which it was not possible to thread the catheter past the obstruction, a pressure gradient varying from 30 to 80 mm. Hg was found at surgery between the left ventricle and the radial artery.

METHODS

Cineangiocardiography was performed during the course of heart catheterization on a table situated 1 meter from the roentgen-ray tube.* The pictures were taken with a 35 mm. camera on Double X film.† The camera was used with the following standards: 80 to 100 kv; 200 ma.; frame exposure time 0.003 second, with rates ranging from 48 to 120 frames per second. The contrast material used was vasurix 30‡ for the selective injections (1–1.5 ml./kg.) and vasurix 50‡ for the intravenous injection (1.5–2 ml./kg.).

The contrast material was injected either intravenously, through a venous cannula (gauge 20/28 in children, 35/40 in adults) inserted into an antecubital vein, or selectively in one of the ventricles, through an Alvarez catheter (No. 7 to 9)§ for the right side, and for the left side, according to Seldinger's technique[26] through a polyethylene or Rapol catheter, with a Gidlund syringe|| (pressure 4 kg./cm.^{2}).

The examination was done in the postabsorptive state, following an intramuscular injection of phenobarbitone 0.10 gm. and of promethazine 0.050 gm.

Thirty-four cineangiographic examinations were carried out by selective injection of contrast material either into the left ventricle: 27 cases, with posteroanterior (PA) incidence in 7, left anterior oblique (LAO) in 1, left lateral (LL) in 1, and right anterior oblique (RAO) incidence in 18; or into the right ventricle: 7 cases, all in RAO incidence. Sixteen cases were studied after an intravenous injection of contrast material, with PA incidence in 3 and RAO incidence in 13 cases. Additionally, 5 cineangiographies were performed after selective injection at the root of the aorta: PA incidence in 2, RAO incidence in 2, and LAO incidence in 1 case.

In 3 cases, a second cineangiocardio-

* Table Navarre, X-ray source Continental, Compagnie Générale de Radiologie, Paris.

† Camera Cameflex, Kodak-France.

‡ Guerbet, St-Ouen, France.

§ Caillon, Mérignac, Gironde, France.

|| Gidlund, A. B. Elema, Stockholm, Sweden.

* From the Clinique Cardiologique, Hôpital Boucicaut, Paris, France.

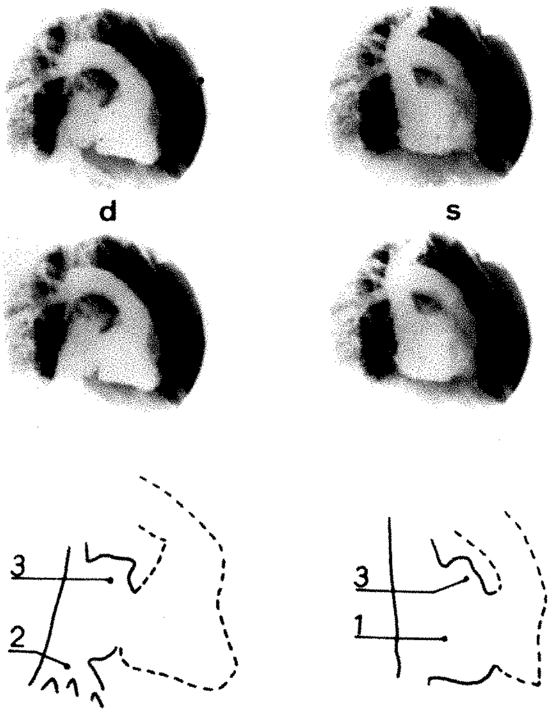


FIG. 1. Aspect of the right atrium. *Top:* Venous cineangiocardiography in right anterior oblique view. Dextrogram: 2 views of ventricular diastole (d) and ventricular systole (s) in the same patient. *Bottom:* Diagram of the right atrium in systole and diastole corresponding respectively to ventricular diastole (d) and systole (s). 1—Atrial enlargement; 2—venous suprahepatic regurgitation; 3—right atrial appendage enlargement. The difference in size of the atrium in systole and diastole indicates the intensity of atrial contraction.

graphic examination was undertaken under isoproterenol infusion in RAO incidence.[3]

Slow speed projection makes it possible to study with greater accuracy both end-systolic and end-diastolic phases, and also to stop on the chosen frame in order to draw the internal contours of the various cardiac chambers.

RESULTS

1. *The right atrium* was studied on 16 cineangiograms (Fig. 1). Its filling was found to be normal in 5 cases, slowed in 10 cases and markedly prolonged in 1 case; in 13 cases a regurgitant flow was seen in the inferior vena cava and in the suprahepatic veins (Fig. 5); this was very marked in 6 cases, with retrograde opacification of the coronary sinus in 1 case. Atrial enlargement was found in 13 cases, while the atrial appendage was enlarged in all cases. Atrial emptying, measured by the number of cardiac contractions necessary for the shadow of the fully filled atrium to disappear, was found to be normal in 7 cases, slow in 7, and markedly prolonged in 2 cases. Right atrial contraction was abnormally vigorous in 14 cases (Fig. 3; and 8).

2. *The right ventricle* was studied in 23 cases, 16 by the venous route and 7 by the selective right ventricular route. Anomalies were noted in both the inflow and outflow tracts.

Anomalies of the anterior margin and of the apex (Fig. 2) were particularly well shown in RAO projections (20 cases). In 9 cases, the diastolic shadow of the right ventricle was practically normal, although its anterior border was slightly irregular and less convex than normally (Fig. 3). In 7 cases, the main changes occurred only during systole, in which the anterior border became straight and vertical and the apex disappeared; however, these modifications may be present in diastole as well (Fig. 4). In systole, the anterior border had a jagged, "geographic map" appearance and assumed a vertical direction from the pulmonary valve down. The inferior border was very short. The whole apical cavity was cut off and the inflow tract had a very small capacity. In 3 cases, the distortion was extreme, the cavity from the tricuspid to the pulmonary valves being reduced to a channel, in which opaque blood flowed very slowly (Fig. 5). Muscle masses separated by pools of contrast medium presented a tumor-like appearance (Fig. 6). In 1 case only were the diastolic and systolic patterns normal.

Three cineangiocardiograms were taken in the PA view. The deformities appeared in 2 cases in systole only: exaggeration of the normal concavity of the anterior border and cutting off of the apex. In 1 case, de-

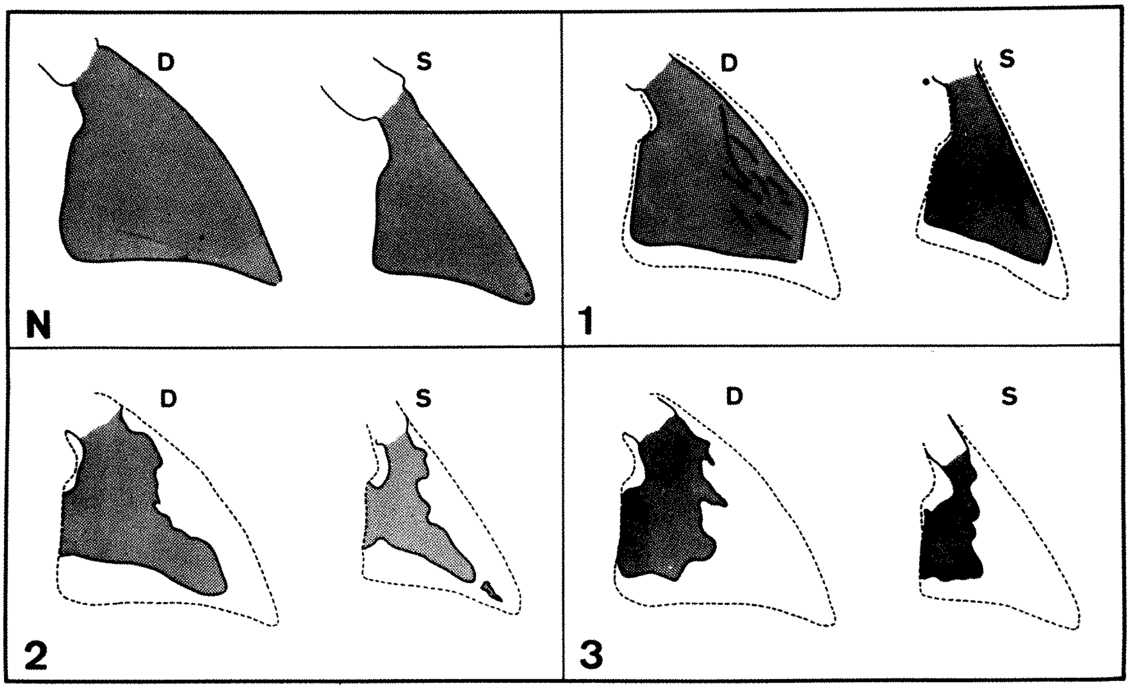


Fig. 2. Diagrammatic representation of the various right ventricular deformities in right anterior oblique view in diastole (D) and systole (S). From left to right: N—normal; 1, 2, and 3—right ventricular deformities of increasing severity. The shaded area represents the right ventricular cavity and the dotted lines its supposed contour in normal subjects.

formities were present both in diastole and systole (Fig. 7).

Mild tricuspid regurgitation was noted in 3 of 7 selective right ventricular cineangiograms.

Deformities of the outflow tract have been noted in 9 cases (RAO view in 7 and

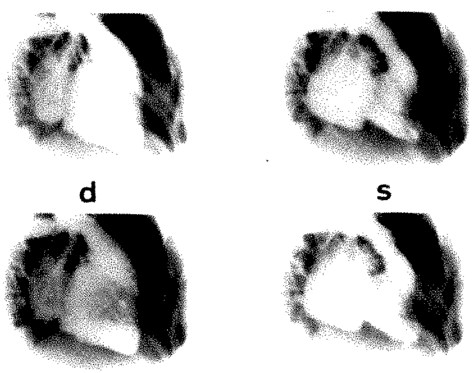


Fig. 3. Venous cineangiocardiogram in right anterior oblique view. Dextrogram: In diastole (d) the right ventricular cavity is practically normal. In systole (s) the anterior border is slightly irregular and concave in its middle part.

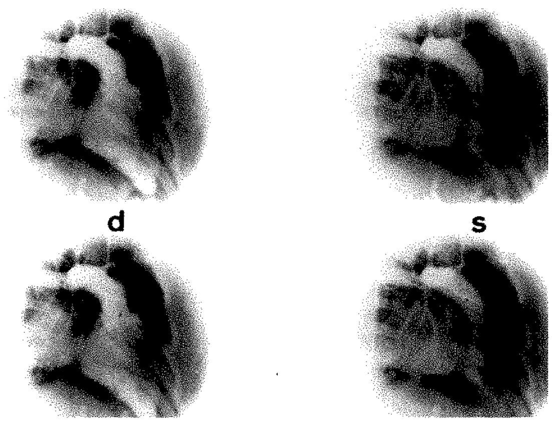


Fig. 4. Venous cineangiocardiogram in right anterior oblique view. Dextrogram: In diastole (d) the anterior border is irregular and markedly concave. In systole (s) considerable reduction of the cavity, with thready and fragmented appearance of its apical part is present.

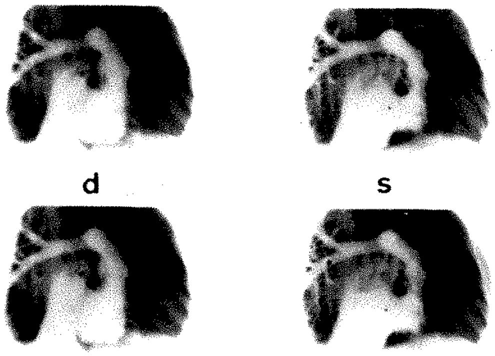


Fig. 5. Venous cineangiocardiogram in right anterior oblique view. Dextrogram: In diastole (d) the right ventricular cavity is reduced in size; its anterior border is rectilinear, with complete disappearance of the apical cavity, where a small pool of opaque medium is trapped. In systole (s) the right ventricular cavity is reduced to a channel. Only the infundibulum retains a normal size.

PA view in 2 cases). They produced in systole the appearance of an infundibular stenosis limited laterally by the relief of the septal and parietal bands of the crista supraventricularis (Fig. 8).

3. *The pulmonary valve, artery and*

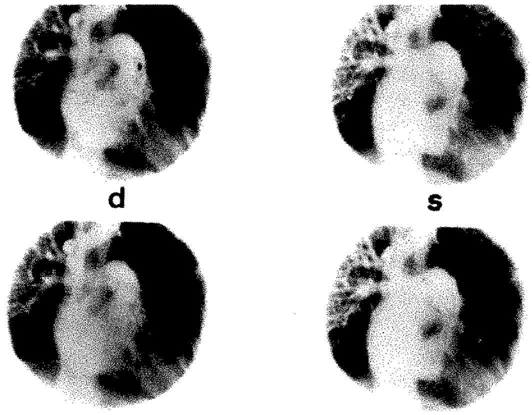


Fig. 7. Venous cineangiocardiogram in the frontal view. Dextrogram: The deformities of the right ventricular cavity are well seen both in diastole (d) and systole (s) but are more difficult to analyze than in the right anterior oblique view.

branches were constantly normal in appearance. Pulmonary vascularization was increased in 1 case only.

4. *The left atrium* (Fig. 9) was studied in the 23 cases of right-sided cineangiograms. Maximal opacification of the left atrium, as a standard of complete filling, was found to occur within normal time

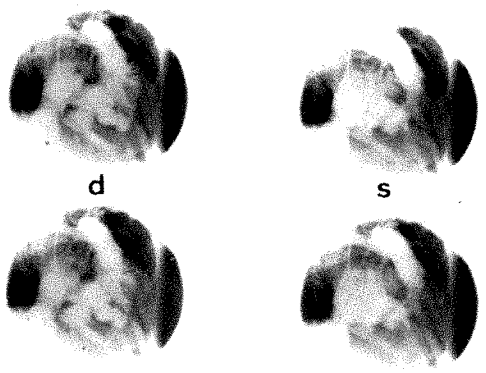


Fig. 6. Venous cineangiocardiogram in right anterior oblique view. Dextrogram: In diastole (d) the right ventricular cavity has an irregular contour resembling a geographic map. In systole (s) the cavity is considerably reduced in size and its irregular contour gives it a pseudo-tumoral appearance.

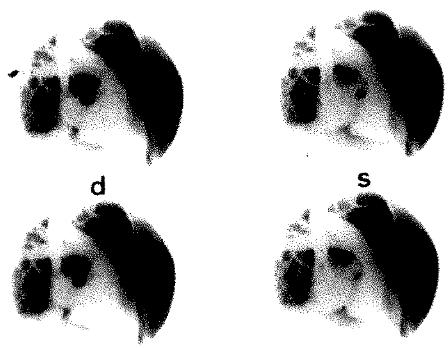


Fig. 8. Cineangiocardiogram in right anterior oblique view. Dextrogram: In diastole (d) the anterior border of the right ventricular cavity is rectilinear and vertical. There is a notch in the outflow tract corresponding to the septal band of the crista supraventricularis. The considerable difference in size of the right atrium during ventricular systole and diastole demonstrates the vigorous atrial contraction.

limits in 11 cases, and delayed in 12. Atrial size was normal in 2 cases only, moderately increased in 12 and definitely increased in 9 cases, but never to a marked degree. The left atrial appendage was well seen in 18 cases, and its volume was prominent in 14 of them (Fig. 11). Emptying of the atrium was always very slow; in 3 cases, it was markedly slowed during more than 20 cardiac cycles. Left atrial contraction was very frequently increased (20 cases).

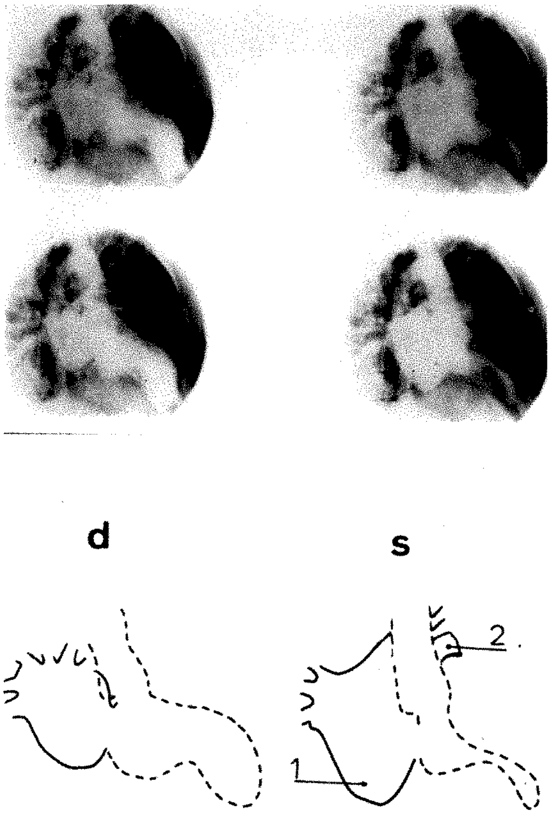


Fig. 9. Aspect of the left atrium. *Top:* Venous cineangiogram in right anterior oblique view. Levogram: 2 views of ventricular diastole (d) and ventricular systole (s) in the same patient. *Bottom:* Diagram of the left atrium in systole and diastole corresponding respectively to ventricular diastole (d) and systole (s). 1—Atrial enlargement; 2—left atrial appendage enlargement. The difference in size of the atrium in systole and diastole indicates the vigor of atrial contraction.

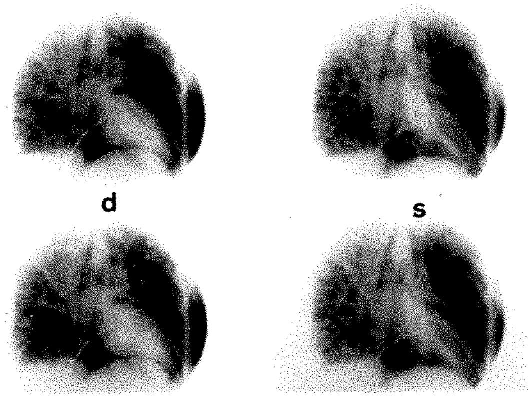
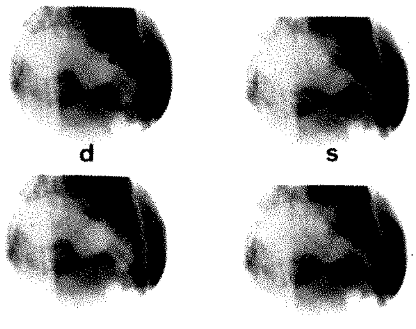


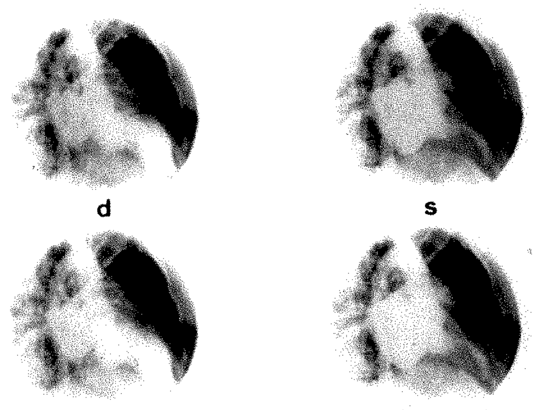
Fig. 10. Venous cineangiocardiogram in right anterior oblique view. Levogram: the left ventricular cavity is normal in diastole.

5. *The left ventricle* was studied particularly in the RAO view (38 cases).

In diastole the left ventricular contour was very close to normal in 11 cases (Fig. 10). In 27 cases, there were definite and suggestive anomalies: an inferior border with inward concavity protruding into the chamber; an anterior border, abnormally convex in its upper third, resulted in a broken great axis of the chamber, which formed a zig zag line opened downwards and backwards (Fig. 11 and 12).

In systole, the configuration of the left ventricular cavity was always abnormal. Two main anomalies were observed, both of which could occur with either a normal or pathologic diastolic pattern: (a) biloculation of the cavity (24 cases), resulting from junction of a concave inferior border and an anterior border concave in its middle third. The cavity assumed an hour-glass appearance with a subvalvular part of normal volume and an apical part, generally exiguous, communicating with each other through a narrow channel (Fig. 11); (b) obliteration of the lower half of the chamber (14 cases), resulting from approximation of the anterior and inferior borders in their distal parts, thus cutting off the corresponding part of the cavity, which is reduced to a grossly triangular subvalvular chamber pointing downwards (Fig. 13). In 6 cases, indentation by the mitral papillary





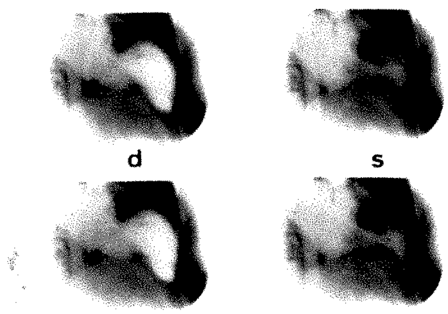


Fig. 11. Venous cineangiocardiograms in right anterior oblique view in 3 patients (2 frames in diastole, and 2 in systole for each patient). Levogram: In diastole (d) deformity of the left ventricular cavity with rupture of its long axis through bulging of its lower border, and increased convexity of its anterior border are seen. The distal part assumes a vertical direction—tongue-shaped appearance. In systole (s) excessive reduction in size and biloculation of the left ventricular cavity, the free wall of which is very thick, are demonstrated.

muscles gave to this subvalvular chamber a trident appearance.

The PA incidence was used in 10 cases. In 1 case only was the diastolic aspect normal; in the other 9, the left border was elongated and more convex than normally and the right border was concave inward in its middle third, sometimes protruding into the cavity. In systole, both deformities described above in RAO incidence could be recognized; *i.e.*, biloculation (7 cases), obliteration (3 cases).

The LAO and LL views were used in 1 case each. In diastole, the anterior border of the chamber did not exhibit the normal convexity, but was displaced posteriorly in its upper half by the septal bulge; the posterior border of the cavity remained distant from the external contour of the heart, thus indicating the considerable left ventricular hypertrophy. A subaortic triangle could be seen in early diastole: its limits are the closed aortic valve superiorly, the septal border anteriorly and the anterior cusp of the mitral valve posteriorly, the latter delineated by the nonopacified left atrial blood (Fig. 14). In systole, the chamber was reduced in its lower half and the subvalvular portion seemed to be free from any narrowing.

6. *Mitral incompetence* was demonstrated in 13 of the 27 cases examined by selective left ventricular injection. In 12 cases, the mitral incompetence was of moderate degree, showing as a central jet, which did not opacify the whole of the left atrium; only once was the regurgitation important, opacifying the whole left atrium and the right pulmonary veins as well.

7. The size of the *coronary arteries* could be assessed in 29 of the 32 selective opacifications of the left ventricle or of the root

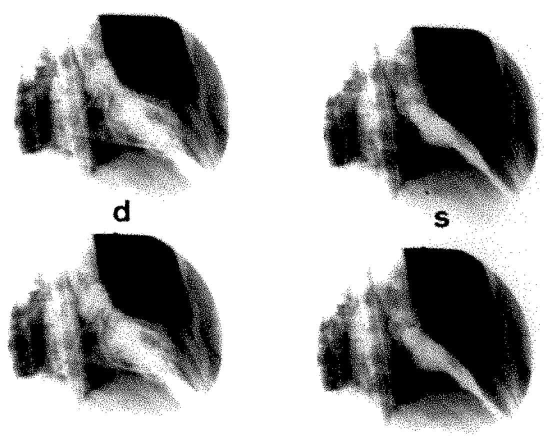


Fig. 12. Selective cineangiocardiogram of the left ventricle in right anterior oblique view. In diastole (d) the subvalvular part is normal in size but the lower half of the left ventricle is narrowed. In systole (s) there is considerable reduction of the cavity which becomes thready in appearance. Besides, the catheter is projected outside the contour of the opaque cavity, being embedded in the heart muscle. This explains the risk of myocardial extravasation of opaque material.

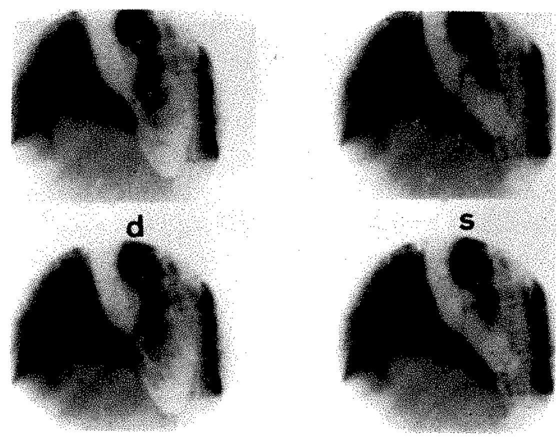


Fig. 14. Selective left ventricular cineangiocardiogram in left anterior oblique view. In diastole (d) the anterior border of the left ventricular cavity is slightly concave at its upper part, and the posterior wall is thickened. There is an appearance of false outflow tract stenosis from the radiolucent image of the anterior leaflet of the mitral valve. In systole (s) the opened aortic semilunar valves are well seen; the stenosis has disappeared, but on the opposite side obliteration of the apex is visualized.

of the aorta; their size was normal in 11 cases and increased in 18 (Fig. 15). Right-sided injections did not usually make it possible to visualize the coronary arteries during the passage of the contrast material to the left side of the heart; nevertheless, they could be well demonstrated in 10 of 23 cases, and their diameter was found enlarged in 6 cases.

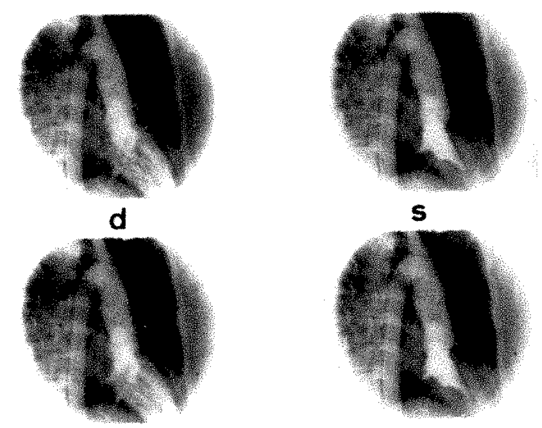


Fig. 13. Selective left ventricular cineangiocardiogram in right anterior oblique view. In diastole (d) the cavity is almost normal. In systole (s) the cavity is reduced to a very small triangular subvalvular chamber, with complete obliteration of the distal part of the left ventricle.

Fig. 15. Selective left ventricular cineangiocardiogram in right anterior oblique view. In systole (s) there is an hour-glass appearance of the left ventricular cavity; the 2 coronary arteries are well seen and are of large size.

8. *The aortic valve cusps*, the *sinuses of Valsalva* were always normal; in 2 cases the ascending aorta was found to be dilated and unfolded.

9. *Isoproterenol infusion* increased the deformities observed during the basal state. During visualization of the right heart (1 case) extreme systolic reduction of the right ventricular cavity resulted in a channel extending from the tricuspid to the pulmonary valve. During left heart visualization (3 cases), the hour-glass pattern was definitely accentuated in 2 cases, and resulted in an obliteration pattern in the third. No mitral regurgitation could be demonstrated in the 2 cases of selective left ventricular opacification.

COMMENTS

Cineangiocardiography has over angiocardiography the advantage of providing a great number of pictures covering the whole cardiac cycle. This technique is particularly valuable for the study of a "functional obstruction," as it enables one to choose the suggestive frames and analyze their chronology.

Selective cineangiocardiography of the left ventricle gives a good opacification of this chamber and permits the detection of mitral incompetence. But it has some disadvantages: the common occurrence of ventricular extrasystoles modifying the left ventricular behavior and the possible contrast material extravasation into the myocardium.[5,12] In our series, this accident was observed in 2 of 27 cases. Venous cineangiocardiography, which is a simpler and less hazardous method, results in a good enough opacification of the left side of the heart, and makes possible the successive study of the 4 chambers and their movements. For these reasons, it seems to be the method of choice.

The RAO view, used in three-quarters of the cases, seems to be the one which gives the best definition of the cardiac chambers; in this view the greater axis plane of the 4 cardiac cavities is almost parallel to the plane of the film. On the dextrogram, it is easy to dissociate the right atrium from the right ventricle, and to identify the indentation marking the site of the tricuspid valve. The antero-septal angle of the right ventricle can be seen and limits anteriorly this cavity by a convex curve. The inflow and outflow tracts are well separated. On the levogram, the left atrium and left ventricle are also well separated, since the mitral ring is perpendicular to the plane of the film. The mitral papillary muscles are visualized separately, as are the apex of the ventricle and its outflow tract.

RIGHT ATRIUM

Right atrial dilatation contrasted with a frequently small right ventricular cavity. Its forcible contraction and slow emptying were related to diminution of right ventricular distensibility. Right atrial enlargement demonstrated by angiocardiography correlated well with the electrocardiographic signs of right atrial hypertrophy in 7 of 13 cases and in all cases with prominent "a" waves on the right atrial pressure tracings (8 to 24 mm. Hg). Tricuspid incompetence, although present in 3 cases, was not accompanied by a prominent "v" wave on the atrial pressure tracings previously recorded. It is probably an artifact due to the passage of the catheter through the tricuspid valve.

RIGHT VENTRICLE

(1) Anomalies of both the anterior margin and the apex were practically constant; they have been noted, more or less clearly, in 19 of 20 dextrograms in RAO view. They were always obvious in systole, but could sometimes be seen also in diastole (10 cases). The RAO view made it possible to study at its best both the topography and the importance of muscular hypertrophy. In the antero-septal angle several muscular elements are found: ansiform band, anterior papillary muscle of the tricuspid valve and many trabeculae carneae. The space lined by these different muscular reliefs on one side and by the interventricular septum and the anterior

wall of the right ventricle on the other was the smaller, the more marked the hypertrophy. This explains both the progressive angiocardiographic deformities of the anterior border, which became first vertical and then concave, and the filling defects. Systolic approximation of the septal, inferior and anterior walls has cut off the apex and the near-by part of the inflow tract. In extreme cases, the right ventricular cavity was reduced to a channel extending from the tricuspid to the pulmonary valve, as confirmed at operation in 2 cases. Exclusion of the right ventricular apex explains the presence of a pressure gradient between the apical portion and the inflow tract.[17]

(2) The patterns of low infundibular stenosis were much less common. They are due to hypertrophy of the muscles lining the crista supraventricularis. The stenosis was often a mild one, and was associated in all cases with a moderate pressure gradient between the outflow and inflow tracts of the right ventricle (average value 18 mm. Hg; range 11–27 mm. Hg). This stenosis might be extremely taut, as in the case reported by Lundquist *et al.*[18] It can be distinguished from congenital infundibular stenosis by its occurrence in systole only; indeed in 8 of 9 cases the infundibular diameter remained during diastole larger than, or equal to, the main pulmonary artery diameter.

(3) There was no correlation between the intensity of the cineangiocardiographic deformities and the presence or absence of electrocardiographic or roentgenologic signs of right ventricular hypertrophy.

LEFT ATRIUM

Left atrial enlargement was frequently observed (21 of 23 cases) but it never was very marked. In the 9 cases in which it was obvious, it could already be seen on standard roentgenograms, or was associated with electrocardiographic signs of left atrial hypertrophy and with a left ventricular end-diastolic pressure exceeding 20 mm. Hg. It might be related to the presence of 2 factors: an eventual mitral incompetence and/or a diminution of left ventricular distensibility, the latter being indicated by the strong atrial contractions and the marked amplitude of the "a" wave on the apex cardiogram.

Mitral incompetence was found in one-half of the cases (13 of 27 cases); this proportion is similar to that of seven series in the literature (47 of 101 cases).[5,8,15,24,27,28,29] Its degree was generally mild to moderate. Its mechanism is under discussion; when marked, mitral incompetence seemed to be related to an anatomic anomaly. The postmortem examination of the only case of massive regurgitation of this series showed hypoplasia of the posterior leaflet of the mitral valve. Similar findings were reported by Lundquist *et al.*,[18] Bjork *et al.*,[1] and by Wigle.[30] However, in the majority of cases, no organic cause could be demonstrated. Mitral incompetence would be functional, in relation to valvular distortion by the septal mass or to displacement of leaflet insertion by the hypertrophied papillary muscles.[29] The occurrence of this mitral incompetence in late systole,[8] and the simultaneous recording of murmurs in both the left atrium and ventricular outflow tract[27] give support to this hypothesis.

LEFT VENTRICLE

Morphologic anomalies of the cavity of the left ventricle were constantly observed. In 28 of the 48 cases examined in the RAO and PA view, a marked concavity of the middle third of the inferior border was already seen in diastole; this resulted in rupture of the great axis of the cavity which formed an angle opened downwards and backwards. This fact has also been noted by Stampbach and Senn,[28] and by Braunwald *et al.*[5] In our series, deformities during systole always occurred, although Braunwald *et al.*[5] reported some cases with normal systolic patterns. The "hour-glass" pattern observed in 31 of 50 cases of the present series was found in 2 of 4 cases by Hansen *et al.*,[15] in all 5 cases of Nordenström *et al.*,[24] in 2 of 28 cases by Braunwald *et al.*,[5] and in 5 of 15 cases by Gravier *et al.*[14]

Such patterns are very suggestive of obstructive cardiomyopathy. Braunwald *et al.*[5] occasionally observed them, although to a lesser degree, in other forms of left ventricular obstruction. Obliteration of the apical region as previously described[10] was noted in 19 of 50 cases in this series; this was rarely reported, except recently by Burchell,[6] and Criley *et al.*[9]

Numerous authors have emphasized the frequency, both in lateral and LAO views, of the "inverted cone" pattern, which would be characteristic of the disease. In fact, this pattern may be observed on the levogram of the normal ventricle during late systole. Its borders are formed by the aortic valve superiorly, the interventricular septum anteriorly and by the anterior mitral leaflet delineated by the non-opacified left atrial blood posteriorly. Although this pattern is more obvious in obstructive cardiomyopathy, it has no diagnostic value.[29] As it is essentially seen during diastole, while the aortic cusps are shown to be closed, it cannot represent the site of obstruction.[6,9,29]

The relationship between the site of obstruction, as seen on angiocardiographic pictures on the one hand and found at catheterization or operation on the other, is still under discussion. Steiner[29] could not, in the majority of cases, determine with accuracy on the angiocardiographic pictures the site of obstruction, but he remarked that in 2 PA angiograms the obstruction could be located much below the aortic valve, leaving a free subvalvular portion. Wigle[31] reported a discrepancy between the sites "where the major septal bulge occurs in the angiograms and where the gradient occurs." According to Braunwald,[4] the point of pressure drop occurred at a distance of 3 cm. below the aortic ring. The stenosis itself was found below the aortic ring at distances of 2–2.5 cm. by Moes *et al.*,[21] 4–5 cm. by Nordenström *et al.*,[24] and well in the middle of the left ventricle in 1 case reported by Hansen *et al.*[15] On operation, Morrow *et al.*[23] located the obstructed area at a distance of 3–5 cm. below the aortic ring. Criley *et al.*[9] in a series of 7 cases studied in RAO view did not observe any significant stenosis of the outflow tract.

In the present series, no stenosis was seen in the subvalvular area; on the contrary, this appeared as the only unstenosed part of the left ventricular cavity. Both systolic obstructive patterns, either "hour-glass" appearance or lower half obliteration of the ventricular cavity, resulted from a more or less complete apposition of the hypertrophied septal mass, the mitral papillary muscles and the free ventricular wall.

It was possible in 1 case to change the hour-glass pattern into the pattern of obliteration of the lower half of the left ventricle by isoproterenol infusion. The latter may thus represent a more severe form of the disease but the spontaneous versatility of the obstruction and the absence of correlation between these 2 angiocardiographic patterns on the one hand and the clinical, electrocardiographic and hemodynamic signs on the other, make it difficult to form a definite opinion.

The site of obstruction, as indicated by cineangiocardiography, correlated well with the data obtained in the 14 cases operated upon. In 7 cases, there was a muscular band, just below the aortic valves, which seemed to represent the upper margin of the septal hypertrophy, and not the actual site of obstruction. Indeed, it overhung either a medio-ventricular muscular ring, which encircled the surgeon's finger during systole (2 cases), or a diffuse muscular hypertrophy which obliterated the lower half of the cavity (5 cases). In 2 cases, mere incision of the subaortic muscular band was not enough, as it left a pressure gradient between the left ventricle and the radial artery; this disappeared when the incision was extended down to the apex. In 3 other cases, a spiral muscular band was responsible for an obstruction of the middle-part of the ventricle; this band started from the interventricular septum, near the apex, and was directed upwards and leftwards,

TABLE II

PER CENT FREQUENCY DISTRIBUTION MATRIX FOR THE COMBINED MISSOURI AND VIRGINIA CASES
(749 patients)

	Atrial Septal Defect Primum	Atrial Septal Defect Secundum	Ventricular Septal Defect	Patent Ductus Arteriosus	Tetralogy of Fallot	Coarctation of Aorta	Pulmonary Valve Stenosis	Aortic Valve Stenosis	Complete Transposition	Rheumatic Heart Disease	Arteriosclerotic Heart Disease	Hypertensive Heart Disease	Myopericardial Disease	Normal Heart
Age														
3 mo. or less	5	2	16	12	18	10	4	0	77	0	0	0	0	0
4 mo. through 5 yr.	48	16	38	43	29	19	48	17	14	0	0	0	4	4
Over 5 yr. through 20 yr.	38	41	33	35	33	43	41	61	9	12	0	3	8	28
Over 20 yr. through 45 yr.	9	20	9	10	20	28	7	22	0	58	4	47	39	58
Over 45 yr.	0	20	4	0	0	0	0	0	0	30	96	50	49	10
Sex														
Male	33	30	37	33	49	62	48	78	59	42	62	53	57	41
Female	67	70	63	67	51	38	52	22	41	58	38	47	43	59
Cyanosis														
Present	10	8	5	10	84	10	4	13	95	1	0	0	0	0
Absent	90	92	95	90	16	90	96	87	5	99	100	100	100	100
Heart Size														
Normal	0	12	17	27	31	52	41	56	5	19	18	25	10	95
Large 1 +	10	33	37	39	33	24	38	35	32	40	64	59	24	5
Large 2 +	33	36	28	19	33	14	17	9	22	31	16	13	38	0
Large 3 +	57	18	18	15	4	10	4	0	41	10	2	3	28	0
Left Ventricle														
Normal	14	76	17	26	92	14	90	22	23	29	16	13	13	95
Large 1 +	48	16	72	59	8	57	10	74	73	43	66	75	43	5
Large 2 +	38	8	11	12	0	29	0	4	4	24	18	12	40	0
Large 3 +	0	0	0	3	0	0	0	0	0	4	0	0	4	0
Right Ventricle														
Normal	0	2	11	24	8	86	10	91	5	27	76	91	26	100
Large 1 +	10	40	44	43	65	9	55	9	36	39	24	6	40	0
Large 2 +	71	50	38	28	25	5	31	0	50	31	0	3	34	0
Large 3 +	19	8	7	5	2	0	4	0	10	3	0	0	0	0
Left Atrium														
Normal	33	96	46	52	94	76	100	83	77	23	100	100	55	97
Large	66	4	54	48	6	24	0	17	23	60	0	0	43	3
Huge	0	0	0	0	0	0	0	0	0	17	0	0	2	0
Right Atrium														
Normal	29	88	96	100	94	100	83	91	82	91	98	100	45	100
Large	71	12	4	0	6	0	17	9	18	9	2	0	55	0
Boot Shape														
Present	0	0	0	0	41	19	14	0	27	1	4	6	2	0
Absent	100	100	100	100	59	81	86	100	73	99	96	94	98	100
Ascending Aorta														
Small	82	66	61	7	15	11	32	0	64	10	0	0	2	0
Normal	18	33	39	90	74	56	68	30	36	61	44	47	76	96
Large	0	0	0	3	11	33	0	70	0	29	56	53	22	4
Arch Size														
Small	79	57	42	8	5	29	42	0	71	9	0	0	2	0
Normal	21	39	58	30	39	47	58	62	29	57	12	6	57	86
Large	0	4	0	62	56	24	0	38	0	34	88	94	41	14
Notched Aorta														
Present	0	0	0	0	0	68	0	0	0	1	0	0	0	0
Absent	100	100	100	100	100	32	100	100	100	99	100	100	100	100
Elongated Descending Aorta														
Present	0	0	0	15	0	70	0	0	0	29	68	60	26	0
Absent	100	100	100	85	100	30	100	100	100	71	32	40	74	100
Infundibulum Sign														
Present	0	2	5	40	0	0	0	0	0	1	2	0	2	1
Absent	100	98	95	60	100	100	100	100	100	99	98	100	98	99
Narrow Heart Base														
Present	0	0	0	0	10	0	0	0	73	2	0	0	0	0
Absent	100	100	100	100	90	100	100	100	27	98	100	100	100	100
Main Pulmonary Artery														
Small	0	0	0	0	49	20	0	9	32	1	0	0	0	0
Normal	5	14	33	28	47	80	10	83	45	82	100	100	94	92
Large 1 +	19	38	37	29	4	0	31	8	23	15	0	0	6	8
Large 2 +	67	26	23	33	0	0	38	0	0	2	0	0	0	0
Large 3 +	10	22	7	10	0	0	21	0	0	0	0	0	0	0
Right Pulmonary Artery														
Small	0	0	0	0	63	0	31	0	0	1	0	0	4	0
Normal	0	16	25	43	35	95	66	96	41	56	66	84	56	96
Large 3 +	100	84	75	57	2	5	3	4	59	43	34	16	40	4
Peripheral Vessels														
Decreased	0	0	0	0	76	0	45	0	0	0	2	0	7	0
Normal	0	2	9	31	20	95	52	91	23	62	64	78	53	93
Increased	100	98	91	69	4	5	3	9	77	38	34	22	40	7
Pulmonary Veins														
Small	0	0	0	0	66	0	37	0	0	0	0	0	10	0
Normal	0	0	29	41	31	100	58	91	25	66	75	87	46	100
Large	100	100	71	59	3	0	5	9	75	34	25	13	44	0
Vessel Disparity														
Present	24	10	70	67	4	0	4	0	18	40	14	6	19	0
Absent	76	90	30	33	96	100	96	100	82	60	86	94	81	100
Reticular Pattern														
Present	0	0	0	0	24	0	7	0	0	4	0	0	0	0
Absent	100	100	100	100	76	100	93	100	100	96	100	100	100	100

(TABLE II *continued on following page*)

TABLE II—(*Continued*)

	Atrial Septal Defect Primum	Atrial Septal Defect Secundum	Ventricular Septal Defect	Patent Ductus Arteriosus	Tetralogy of Fallot	Coarctation of Aorta	Pulmonary Valve Stenosis	Aortic Valve Stenosis	Complete Transposition	Rheumatic Heart Disease	Arteriosclerotic Heart Disease	Hypertensive Heart Disease	Myopericardial Disease	Normal Heart
Kyphoscoliosis														
Present	0	8	5	5	27	5	7	0	10	6	16	10	4	3
Absent	100	92	95	95	73	95	93	100	90	94	84	90	96	97
Rib Notching														
Present	0	0	0	0	0	29	0	0	0	1	0	0	2	0
Absent	100	100	100	100	100	71	100	100	100	99	100	100	98	100
Hyperexpansion														
Present	38	6	44	52	16	14	10	4	55	14	30	13	6	11
Absent	62	94	56	48	84	86	90	96	45	86	70	87	94	89
Kerley's Lines %B <														
Present	0	0	0	0	0	0	0	0	0	19	2	0	11	0
Absent	100	100	100	100	100	100	100	100	100	81	98	100	89	100
Mitral Valve Area Calcification														
Present	0	0	0	0	0	0	0	0	0	17	0	0	0	0
Absent	100	100	100	100	100	100	100	100	100	83	100	100	100	100
Aortic Valve Area Calcification														
Present	0	0	0	0	0	0	0	8	0	8	8	0	0	0
Absent	100	100	100	100	100	100	100	92	100	92	92	100	100	100
Aortic Calcification														
Present	0	0	0	0	0	0	0	0	0	12	65	17	12	0
Absent	100	100	100	100	100	100	100	100	100	88	35	83	88	100
No. of Cases	21	50	57	42	49	21	29	23	22	226	50	32	53	74

pared to half the transverse thoracic diameter measured at the dome of the right hemidiaphragm. A normal heart size has a transverse diameter less than one half the transthoracic diameter (Fig. 1). One plus enlargement of heart size is present when the transverse cardiac diameter is equal to half the transverse thoracic diameter (Fig. 2), 2+ enlargement is present when the cardiac diameter is greater than half the transthoracic diameter (Fig. 3), and 3+ enlargement indicates the transcardiac diameter to be much larger than half the transthoracic diameter (Fig. 4).

Left and right ventricular enlargement is illustrated in Figures 5, 6, 7 and 8. One plus

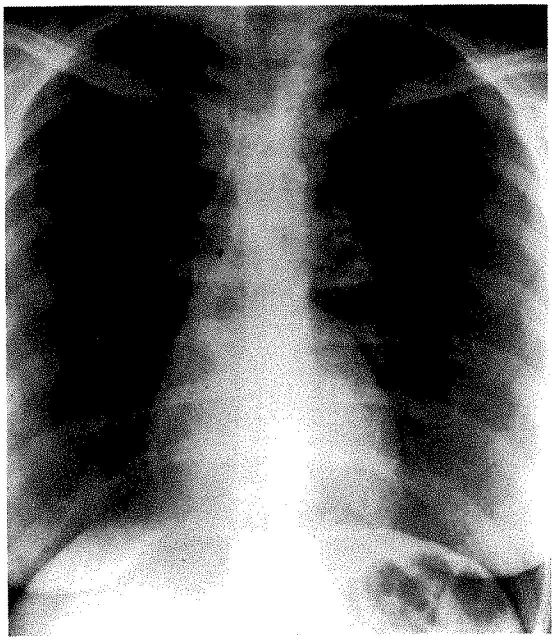


FIG. 1. Patient with tetralogy of Fallot with normal heart size, enlarged ascending aorta, small main pulmonary artery segment, small right pulmonary arteries, and decreased peripheral vessels.

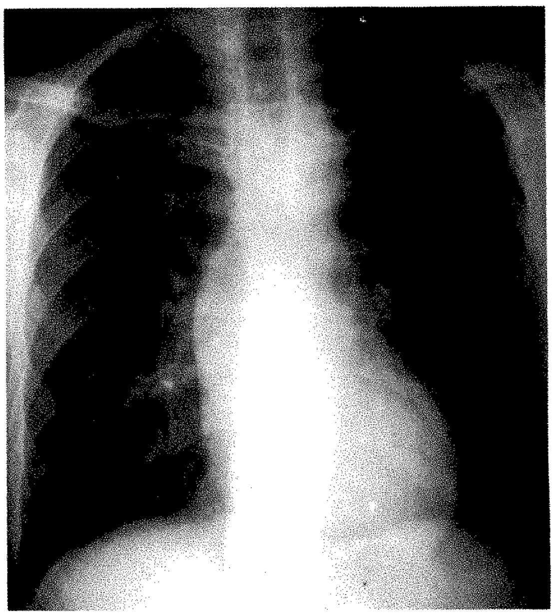


FIG. 2. Patient with aortic stenosis and insufficiency with 1+ heart enlargement. There is enlargement of the ascending aorta, aortic arch and elongation of the descending aorta. The right main pulmonary arteries and peripheral vessels are normal.

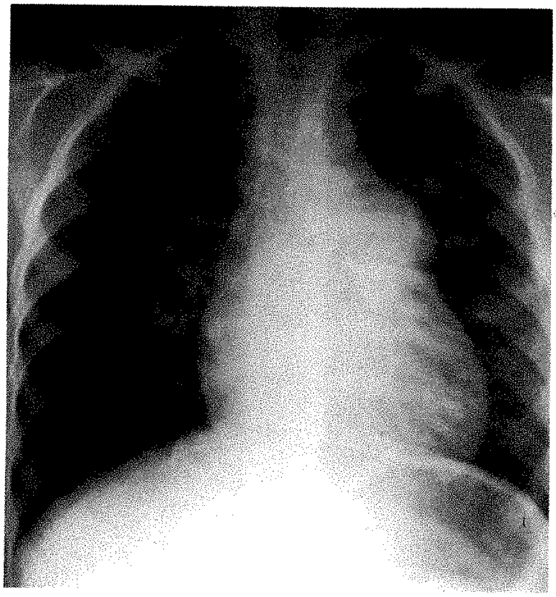


Fig. 3. Patient with a patent ductus arteriosus showing 2+ heart enlargement. The main pulmonary artery segment is 3+ enlarged and the right main pulmonary arteries are large. Peripheral vessels are increased and disparity of vessel size is present.

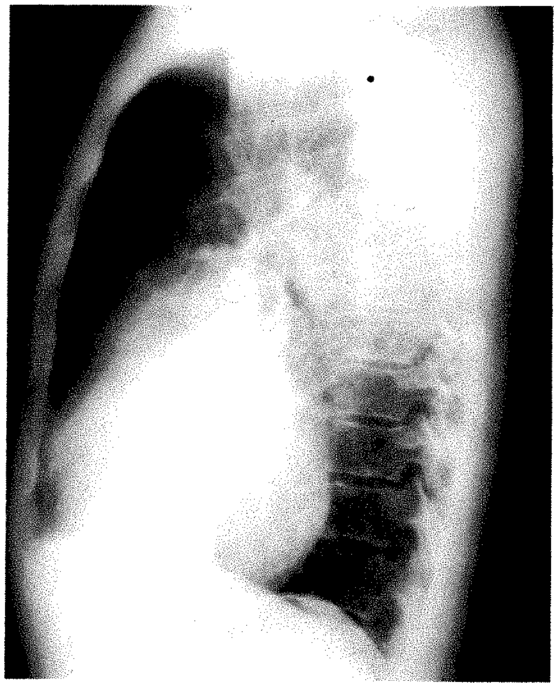


Fig. 5. There is 3+ enlargement of the left ventricle and a normal right ventricle.

and 2+ enlargement of the right ventricle (Fig. 6 and 7) indicate minimal and moderate enlargement of this chamber. Three plus enlargement of the right ventricle (Fig. 8) is present when enlargement of the right

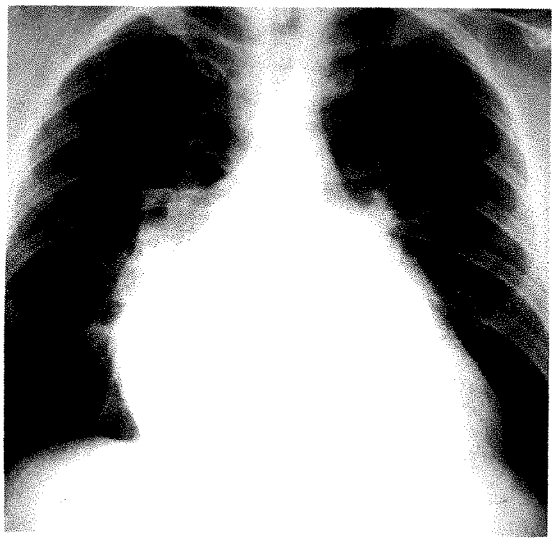


Fig. 4. Patient with mitral insufficiency and stenosis demonstrating 3+ enlargement of the heart and a huge left atrium. The main pulmonary artery segment is normal.

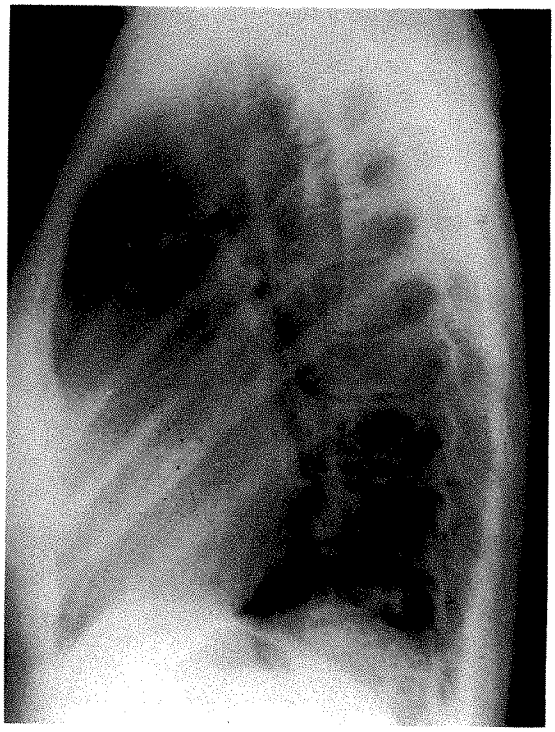


Fig. 6. One plus enlargement of the right ventricle. The posterior heart border intersects the inferior vena cava at the level of the left hemidiaphragm indicating 1+ left ventricular enlargement.

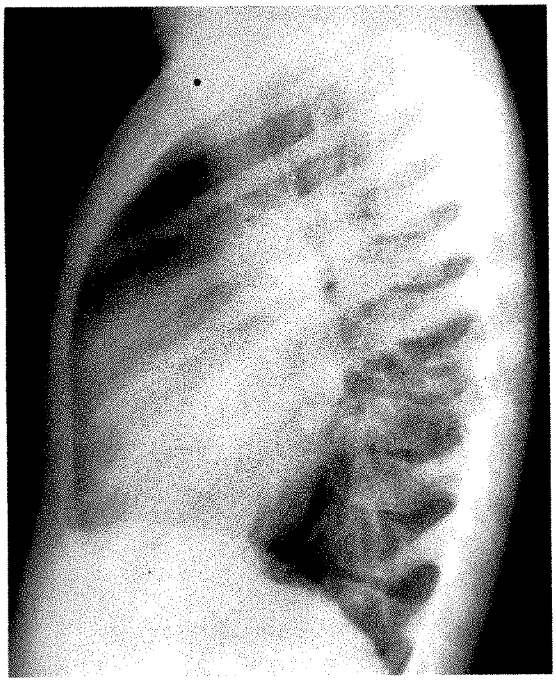


Fig. 7. There is marked enlargement of the right ventricle (2+) without bowing of the sternum. The posterior heart border intersects the left hemidiaphragm behind the inferior vena cava (2+ enlargement).

ventricle has produced outward bowing of the sternum. Left ventricular enlargement is based on the relationship of the posterior heart border to the inferior vena cava at the point where the inferior vena cava intersects the left hemidiaphragm. Three plus enlargement of the left ventricle (Fig. 5) is infrequently identified: this is, in part, because cardiac diseases that produce very large left ventricles are frequently associated with right ventricular enlargement. Enlargement of the right ventricle results in posterior displacement of the heart thus making a precise evaluation of the left ventricular size difficult.

A large left atrium is present when this chamber is big but does not elevate the left main bronchus or produce widening of the carina (Fig. 9). Elevation of the left main bronchus signifies a huge left atrium (Fig. 4). Right atrial enlargement is considered present when the right atrial border overlaps the intermediate bronchus.

Figure 2 demonstrates a large ascending aorta, a large aortic arch, and elongation of the descending aorta. The notch sign[1] of coarctation with poststenotic dilatation of the descending aorta is present in Figure 10. The infundibulum sign[5] is illustrated by the arrow in Figure 11. The base of the heart refers to the relationship of the main pulmonary artery to aortic arch. In complete transposition of the great vessels, these structures have an anteroposterior relationship resulting in a narrow heart base.

The size of the undivided main pulmonary segment was graded as small (Fig. 1), normal (Fig. 4), or large (Fig. 3 and 11). Three plus enlargement of the main pulmonary artery was indicated by marked convexity of this structure (Fig. 3).

The right main pulmonary arteries refer to the size of these major vessels within the medial third of the right lung. They may be decreased (Fig. 1), normal (Fig. 2), or increased (Fig. 3). Peripheral vessel size re-

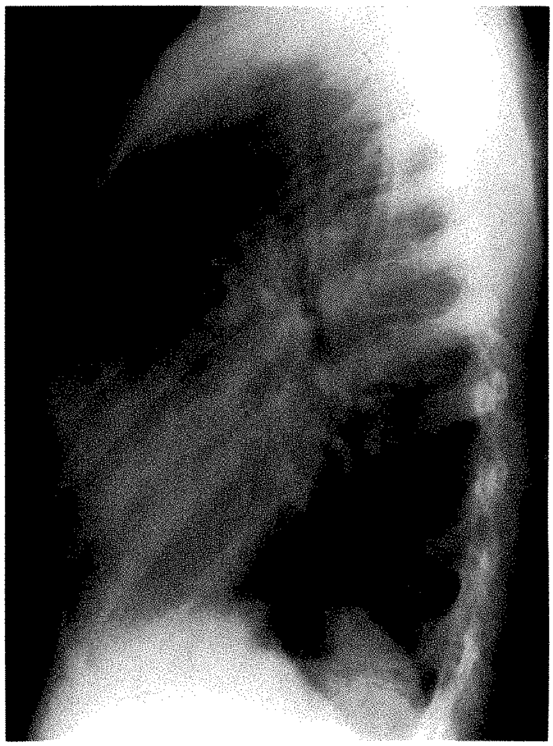


Fig. 8. The left ventricle is normal but there is 3+ right ventricle enlargement.

fers to the vasculature in the middle half of the lung. It may be decreased (Fig. 1), normal (Fig. 2), or increased as in left to right shunts (Fig. 3). An attempt was made to determine pulmonary vein size as it approached the left atrium within the right lung (Fig. 2). Peripheral vessel disparity is demonstrated in Figure 3 and indicates the disproportionate tapering of arteries as they extend peripherally from the hilar area.

Hyperplastic bronchial arteries, as seen with tetralogy of Fallot, frequently produce a reticular pattern in the middle and peripheral portions of the lung (Fig. 1). Hyperexpansion refers to flattening of the hemidiaphragm as seen on the lateral chest roentgenogram.[10] Kerley's "B" lines are short (1 to 2 cm.), uniform, thin lines located in the periphery and base of a lung perpendicular to the lateral chest wall (Fig. 12).[4] An evaluation of valve area calcification from plain chest roentgenograms is difficult but if calcification was definitely identified, the proper notation was made.

RESULTS AND DISCUSSION

The per cent frequency distribution or incidence matrix for the 25 roentgenographic signs as they described the 14 different heart disease categories are presented in Table II. The University of Missouri and University of Virginia cases have been combined so that the matrix represents the total experience from 749 patients. The number of cases in each diagnostic category is listed at the bottom of the matrix.

The 148 cases from the University of Virginia were diagnosed using the frequency distribution matrix compiled from the 601 University of Missouri patients. The University of Missouri matrix was slightly modified in that a few zeros were replaced with 1 per cent. The reason for this is that if a given case is typical of a certain disease category but has a single finding not contained in the computer's memory, the presence of a zero probability will throw the case out of that category. Example: All proved cases of pulmonary valve stenosis (PVS) had at least 1+ enlargement of the right ventricle. An unknown case was seen which was typical for PVS except that the right ventricle was roentgeno-

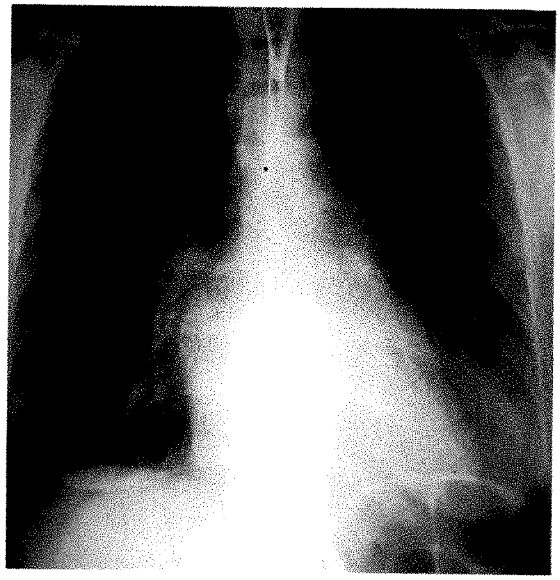


Fig. 9. The left atrium is large and there is 2+ enlargement of the heart. One plus enlargement of the main pulmonary artery is present. Note the apparent elongation of the descending aorta which is actually due to lateral displacement by the posterior heart. This patient has pure mitral stenosis.

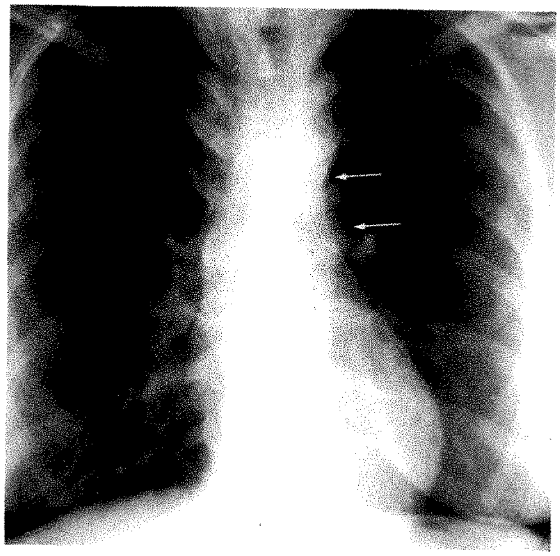


Fig. 10. Patient with coarctation demonstrating rib notching and a notched aorta (upper arrow) with poststenotic dilatation of the aorta (lower arrow).

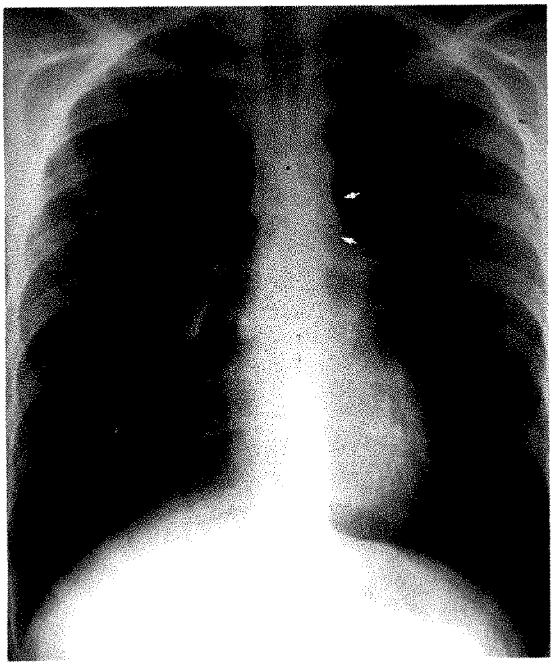


FIG. 11. Patient with patent ductus arteriosus demonstrating the infundibulum sign (arrows). There is 2+ main pulmonary artery enlargement.

graphically normal. Since no previous case of PVS had a normal right ventricle, a zero was present in this location in the matrix and a diagnosis of PVS was immediately excluded by the computer.

Using the unmodified Missouri matrix and Bayes' Theorem with the assumption of variable independence, the computer diagnosed 54 per cent of the Virginia cases correctly. With the slightly modified Missouri matrix, the computer diagnosed 67 per cent of the cases. The discrepancy between these figures emphasizes the importance of modifying the computer's experience with the radiologist's understanding of the pathophysiology of heart lesions and his broader experience.

Using the Missouri series of proved cases, the Virginia cases were diagnosed by the statistically more sophisticated method of linear dependence. The correct diagnosis was obtained in 39 per cent of the total series and in 45 per cent of the patients with congenital heart disease.

The Virginia cases were then added to the Missouri matrix (Table II) and the Virginia cases diagnosed against this new matrix. Assuming independence of roentgenographic signs, the computer diagnosed 70 per cent of 148 cases correctly and 81 per cent of the congenital lesions correctly. The method of linear independence was right in 76 per cent of the total cases and 80 per cent of the congenital lesions.

These results are actually quite satisfactory particularly for a screening process using only posteroanterior and lateral roentgenograms of the chest. However, two questions remain. First, why does the computer do better diagnosing congenital heart lesions rather than the total series; and second, why does the assumption of independence give more correct diagnoses for unknown cases than the method assuming linear dependence?

The answer to the first question is that all of the congenital heart lesions studied have been uncomplicated defects with rela-

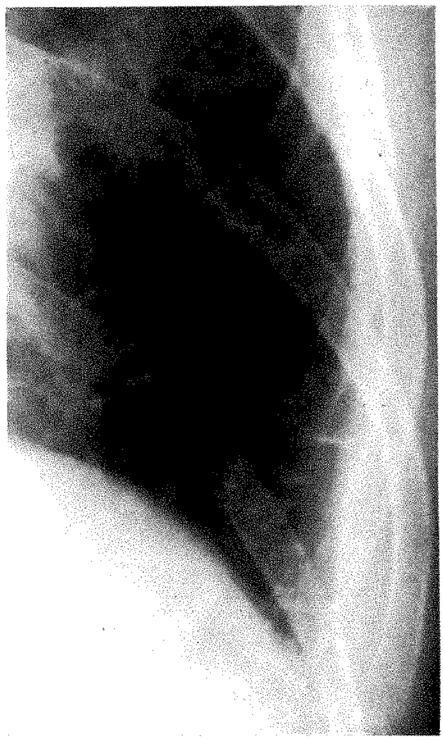


FIG. 12. Kerley's "B" lines.

tively specific physiologic and pathologic abnormalities that reflect themselves with rather characteristic anatomic changes. An exception is the difficulty experienced in differentiating ventricular septal defect from patent ductus arteriosus—both high pressure shunts—in infants. Rheumatic heart disease is sometimes characteristic, but aortic valve lesions are frequently non-specific and can mimic hypertensive heart disease, arteriosclerotic heart disease, or congenital aortic valve stenosis and *vice versa.*

The failure of the method of linear dependence to reach more correct diagnoses in the series of unknown cases can be explained by noting that this method requires that more information be extracted from the proved case material. Whereas the method of independence requires the proved cases to yield estimates of the frequencies for the 28 findings found in the worksheet; the method of linear dependence requires, in addition, estimates of the covariances of every pair of findings. Since there are 406 such pairs, the method of linear dependence requires more than ten times as much descriptive information about each disease as does the method of independence. This means that the computer has a much greater chance of making errors. If the number of proved cases for each disease is large enough these errors should be infrequent; but if the number of cases is insufficient, the computer will create a diagnostic model which is characteristic only of the series of proved cases rather than of the disease as a whole. This in turn implies that although the computer will do quite well in diagnosing a case exactly like a case seen previously, it will do poorly with unknown cases.

Our results indicate that the number of proved cases available to us is not as yet sufficient to provide adequate diagnostic information for sophisticated computer diagnosis. This explains why, assuming roentgenographic sign independence, the computer diagnosed only 54 per cent of the Virginia cases using the unmodified Missouri matrix; but obtained the correct diagnosis in 70 per cent of the cases when the Virginia series was included in the set of known cases. The greater discrepancy from 39 per cent to 76 per cent using the method of linear dependence reflects the greater chance for error inherent in this method.

It is clear that some method of extending the computer's experience is necessary. Probably the best way to accomplish this would be to expand the series of proved cases so that several hundred cases of each disease were available. An alternative method would be to incorporate the radiologist's experience into the model. Using the method of independence, this is relatively easily accomplished by modifying the frequency distribution matrix. A method for similarly modifying both the frequency distributions and covariances of the roentgenographic signs could be of considerable value in improving the method of linear dependence, but no such procedure is presently available.

CONCLUSION

The posteroanterior and lateral chest roentgenograms of 749 patients with one of 13 different heart diseases or with a normal heart have been reviewed. Six hundred and one patients were from the University of Missouri Medical Center. A test series of 148 unknown cases from the University of Virginia was also analyzed.

Twenty-five roentgenographic signs were evaluated for all 749 patients. Using these roentgenographic data, plus the age, sex and presence or absence of cyanosis, the computer compiled a frequency distribution matrix. The test series of 148 unknown cases was diagnosed by the computer using the data from the University of Missouri Medical Center patients. Two Bayesian methods were used by the computer; one assuming independence of roentgenographic signs and the other assuming linear dependence of roentgenographic signs. The results are presented and discussed.

The worksheet for recording data, the frequency distribution matrix, and the descriptive and illustrative examples of each roentgenographic sign represent our Public Model. All radiologists can use this Public Model to systematically analyze and diagnose heart disease.

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THE EFFECTS OF UNILATERAL THORACIC IRRADIATION ON PULMONARY BLOOD FLOW*

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THE world's medical literature contains many articles dealing with radiation pneumonitis and fibrosis which have appeared since the original description by Groover *et al.*[6] of certain symptoms, signs, and roentgenographic changes incident to radiation therapy of the chest following mastectomy. A recent review outlines the highlights of this extensive literature.[11] Attention has been concentrated on the incidence, severity, pathology, and prevention of radiation damage to the lung. Physiologic investigations have been carried out primarily on the ventilatory capacity and the diffusing capacity because these functions are readily measured.

Physiologic studies in dogs with radiation pneumonitis and fibrosis have indicated that a complex change is produced in lung function. Evidence has been presented showing that a so-called alveolar-capillary block could not account for the decreased gas exchange in the damaged lung.[15] Finley *et al.*[3] have shown that impaired diffusion is probably due in large part to nonuniform distribution of gas and blood in the lungs and pulmonary arterial-venous shunting, rather than thickening of the alveolar and capillary walls. The circulatory component of gas exchange in the radiation damaged lung has not received the attention it deserves. This report concerns the effects of thoracic irradiation on the pulmonary circulation as investigated experimentally in dogs.

MATERIAL AND METHOD

Three mongrel dogs received a calculated mid-lung dose of 3,000 r directed to the entire right lung, but sparing the left lung, in 3 doses over a 5 day period. The radiation was equally divided between anterior and posterior portals on alternate days using cobalt 60 teletherapy.

The lungs were studied prior to irradiation and at frequent intervals up to 393 days after irradiation with thoracic roentgenograms and lung scans. The scans were obtained after the intravenous injection of 100 microcuries of I^{131} macroaggregated human albumin. No allergic reactions to the small quantities of human albumin were noted. Pulmonary arteriograms were obtained at about 400 days after irradiation in each case. The lungs were examined grossly and microscopically following the arteriograms.

Relative pulmonary blood flow to each lung was calculated by the method of Lopez-Majano *et al.*[8] Scan density was determined in three regions of each lung by a photometer with a 1 inch diameter porthole. The total scan density of the right lung was compared to the total scan density of both lungs, and values for estimated percentage artery perfusion of the right lung were calculated.

RESULTS

All scans were made with the range of the photorecorder set to give as near a linear response as possible from background to highest isotope concentration in the lung fields. Several test scans with known concentrations of I^{131} using these settings gave a density curve which was linear on semi-log paper. This curve was used to correct the density readings of the lung scans prior to calculation of the percentage perfusion of the irradiated lung.

The estimated blood flow to the right lungs prior to irradiation averaged 49.5

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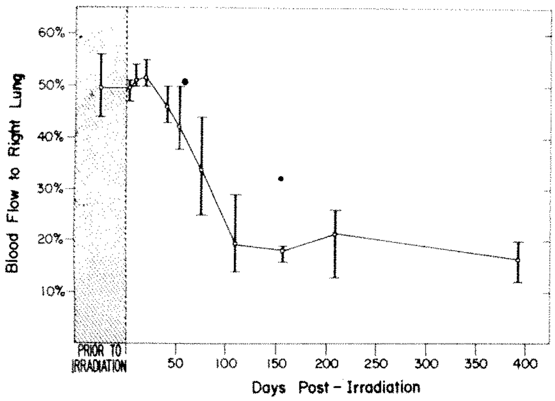

Fig. 1. Estimated percentage of pulmonary blood flow to the irradiated right lung. The average values for the 3 animals are indicated by the solid line and the range of values by the vertical brackets.

per cent of total lung perfusion in 8 determinations on the 3 experimental animals. The range of values was 44 per cent to 56 per cent. Two animals showed a decrease to 38 per cent and 39 per cent perfusion at 52 days following completion of irradiation, and all animals had decreased perfusion at 109 days. The average values for estimated pulmonary blood flow to the irradiated lung and the range of values in the 3 animals are illustrated in Figure 1. Most of the loss of perfusion is noted by 109 days with little subsequent change.

The chest roentgenograms usually showed a slight alveolar infiltration resembling bronchopneumonia before a definite change occurred in the lung scan. This first change was noted at 44 or 52 days after irradiation and usually proceeded to complete or patchy consolidation of the irradiated lung. The peak of infiltration was seen at 76 or 109 days. A considerable loss of lung volume was associated with the consolidation. Most of the consolidation cleared by 211 days, but the loss of volume persisted. The changes noted on the roentgenograms and scans are illustrated in Figures 2 to 8.

The pulmonary arteriograms demonstrate dramatically the loss of volume of the irradiated lung. The right upper lobe artery is small and distorted, ending close to the hilum (Fig. 10 and 11). The over-all size of the segmental and subsegmental arteries is markedly reduced, and the lobular arteries are proportionally reduced in size. In some areas, the lobular arteries are not visualized. The failure to demonstrate these vessels might be related to their size and the limitations of resolution. The terminal arteries and arterioles were not visualized.

The pathologic specimen of the lungs

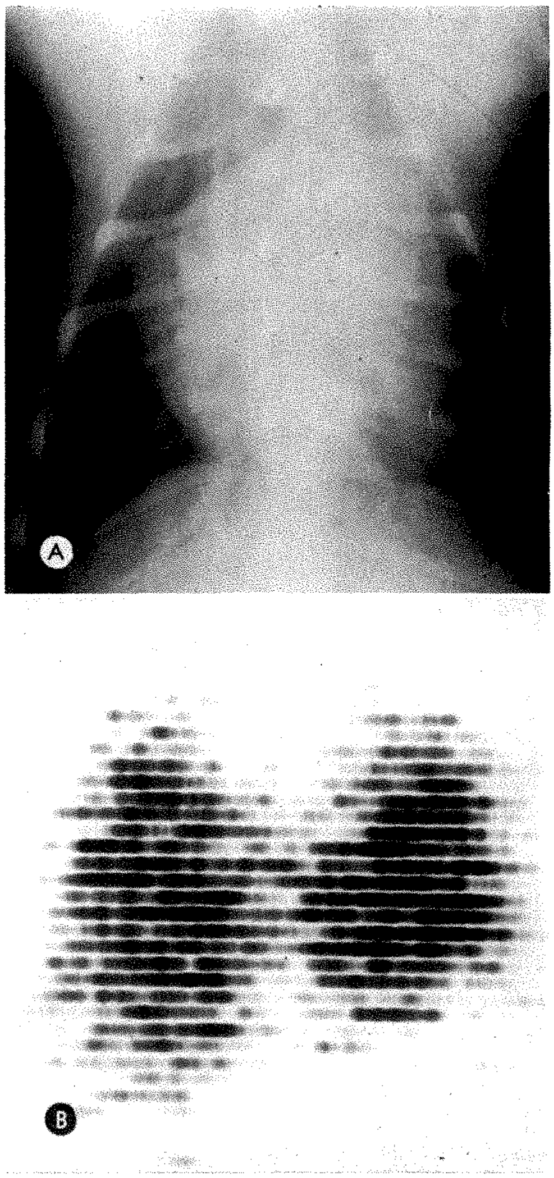

Fig. 2. (*A*) Chest roentgenogram and (*B*) scan on Dog 1 prior to irradiation.

showed marked fibrosis and atrophy in some areas, particularly in the upper and cardiac lobes (Fig. 9). The nonirradiated lung and heart shifted to the right to compensate for the loss of volume. The irradiated lower lobes and intermediate lobes

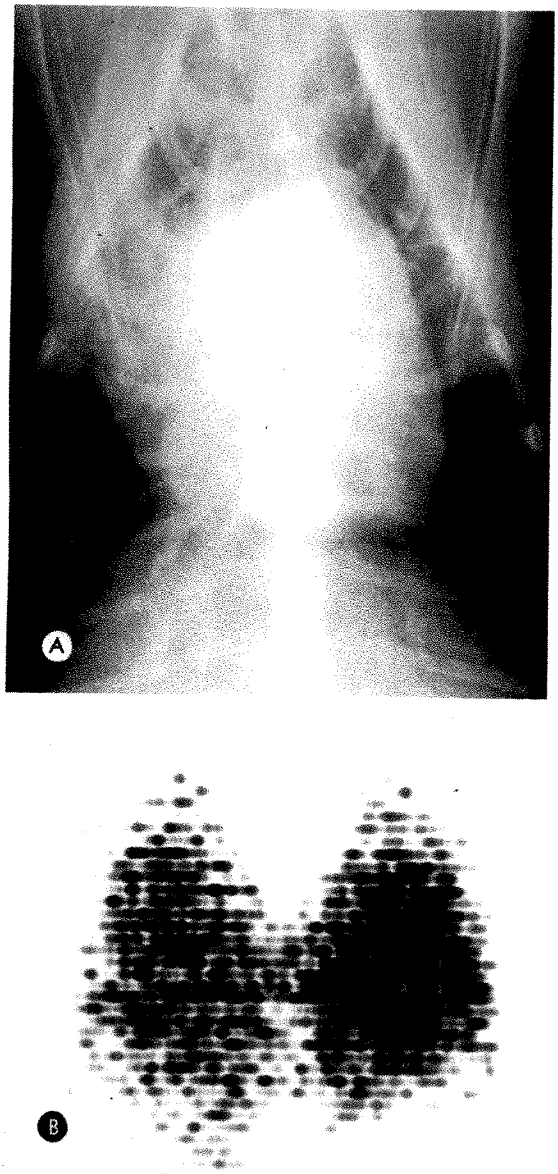

Fig. 3. (*A*) Chest roentgenogram and (*B*) scan on Dog 1, 52 days after irradiation, when changes first became evident. Note the slight shift of the heart toward the irradiated side and the indistinct right heart border. Although the perfusion appears greater in the left lung, a significant change has not occurred according to the photometric evaluation.

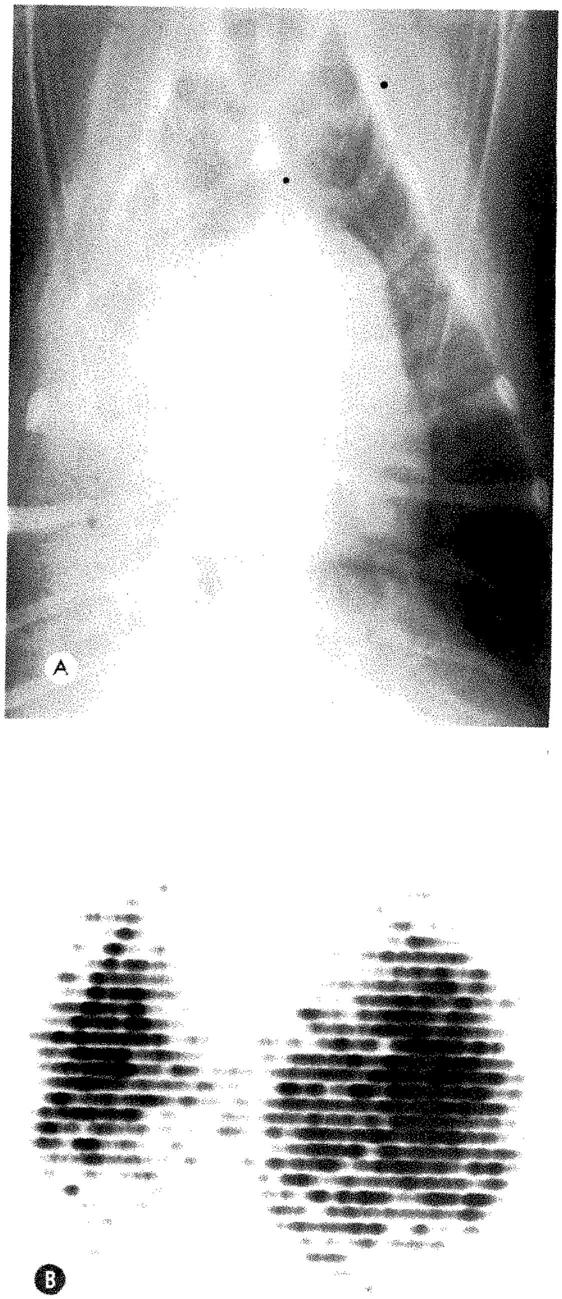

Fig. 4. (*A*) Chest roentgenogram and (*B*) scan on Dog 1, 76 days after irradiation. The right lung is almost totally consolidated and perfusion is somewhat diminished.

showed less severe changes in general. One dog had a moderate infestation of heart worms and another had several heart worms. The scans, roentgenograms, and

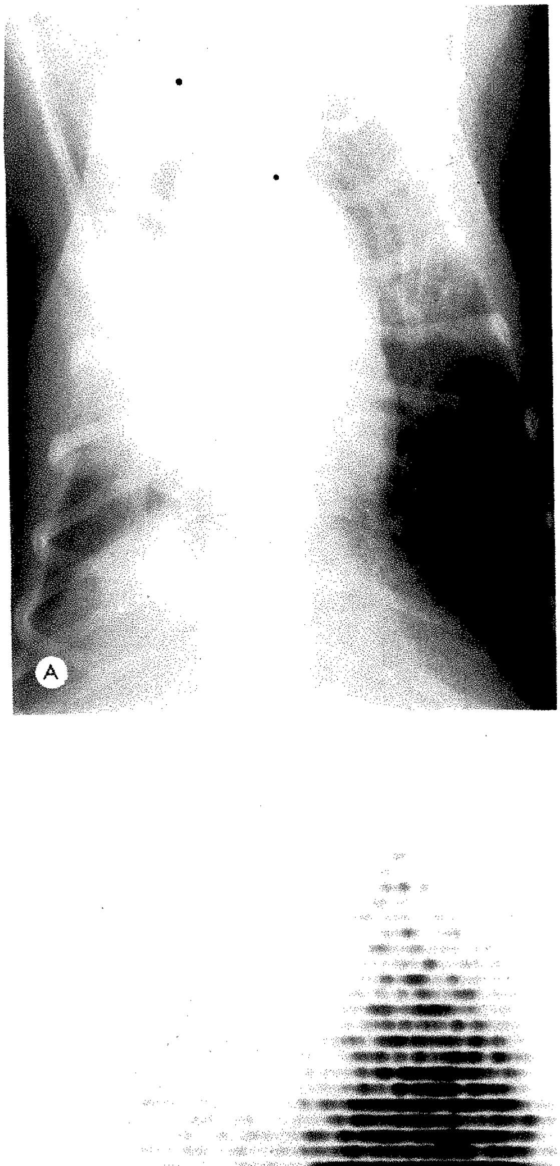

FIG. 5. (*A*) Chest roentgenogram and (*B*) scan on Dog 1, 153 days after irradiation. Much of the infiltration has resolved, but a marked loss of volume is apparent. The right lung receives only 20 per cent of the pulmonary blood flow.

pathologic changes were the same whether or not worms were present. The right atrial appendage was fibrotic with obliteration of the lumen in all 3 animals. The

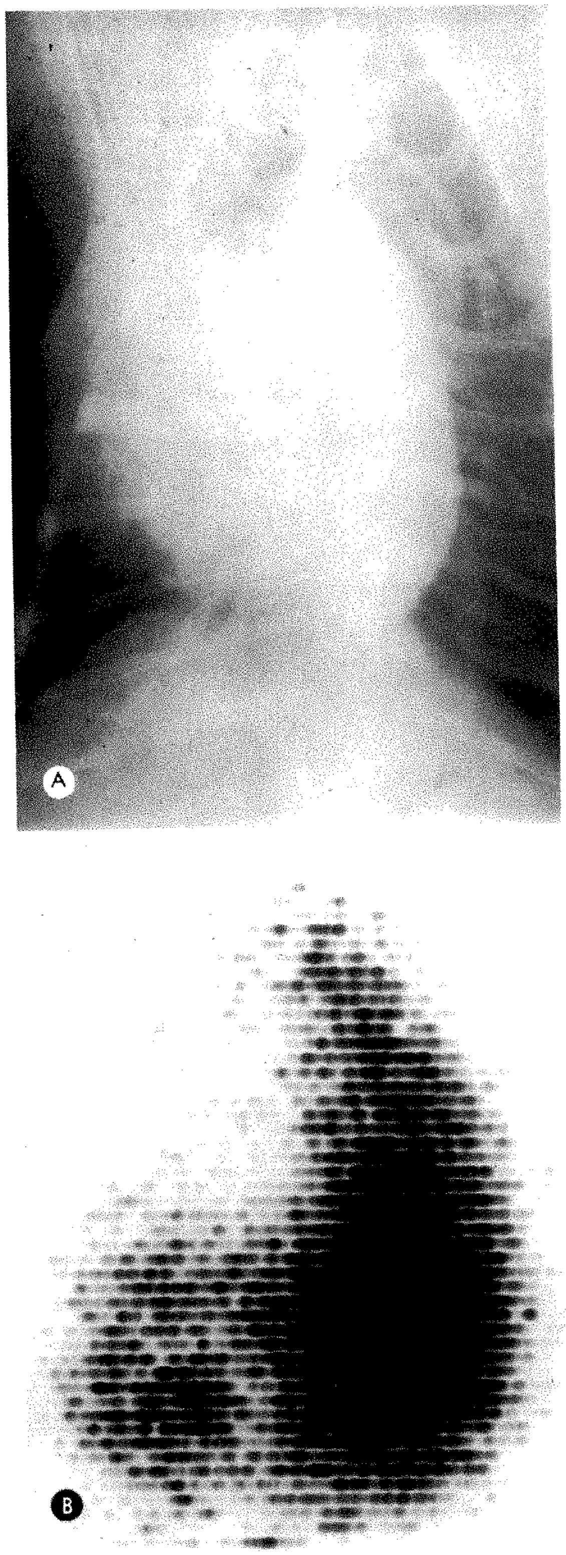

FIG. 6. (*A*) Chest roentgenogram and (*B*) scan on Dog 1, 393 days after irradiation. The perfusion remains at about 20 per cent.

right ventricle showed no change. Microscopically, the changes consisted of variable thickening of the alveolar walls, pleura, and vessel walls. In some areas the lung architecture was essentially preserved, but in other adjacent areas almost all normal features were destroyed. Bizarre, enlarged

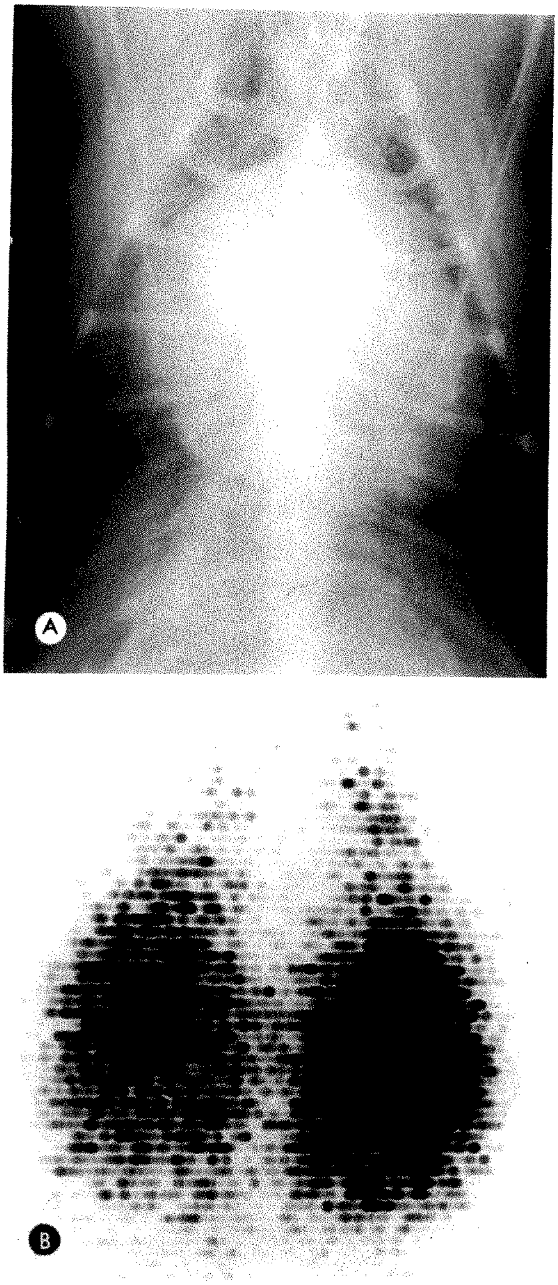

Fig. 7. (*A*) Chest roentgenogram and (*B*) scan on Dog 2, 44 days following irradiation of the right lung. The roentgenogram is unchanged, but the scan shows a slight reduction in flow on the right.

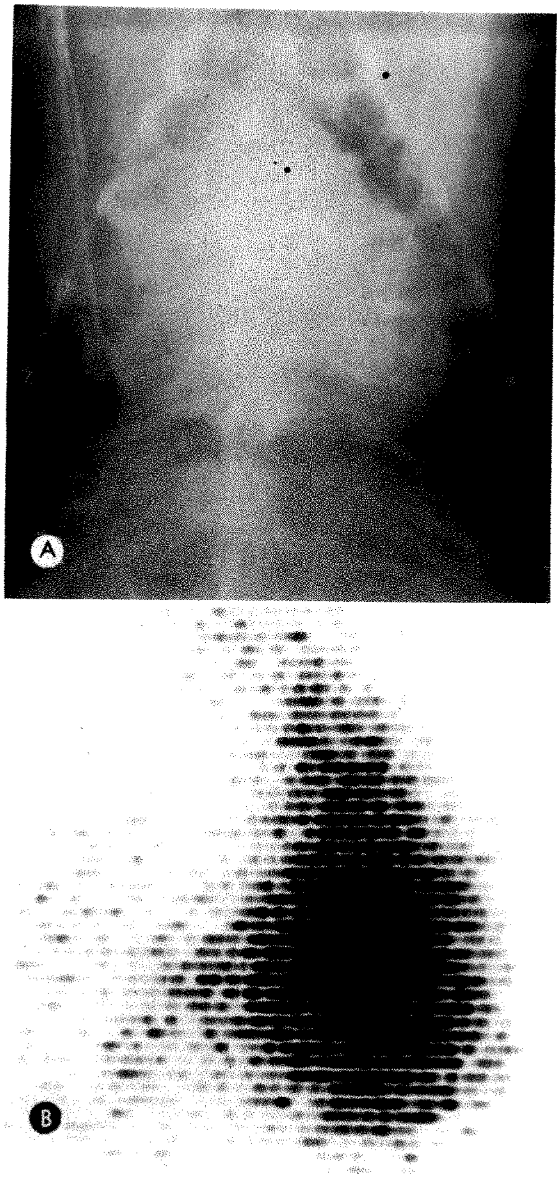

Fig. 8. (*A*) Chest roentgenogram and (*B*) scan on Dog 2, 393 days after irradiation. Only 14 per cent of pulmonary blood flow goes to the right lung.

alveolar lining cells were prominent. Marked thickening of the media and intima was apparent in a few pulmonary vessels in each animal. The features are those described by previous investigators.[7,12,17,18]

DISCUSSION

In a previous communication, indirect techniques showed that the pulmonary blood flow diminishes in irradiated lung tissue, as do other measured functions.[15] The

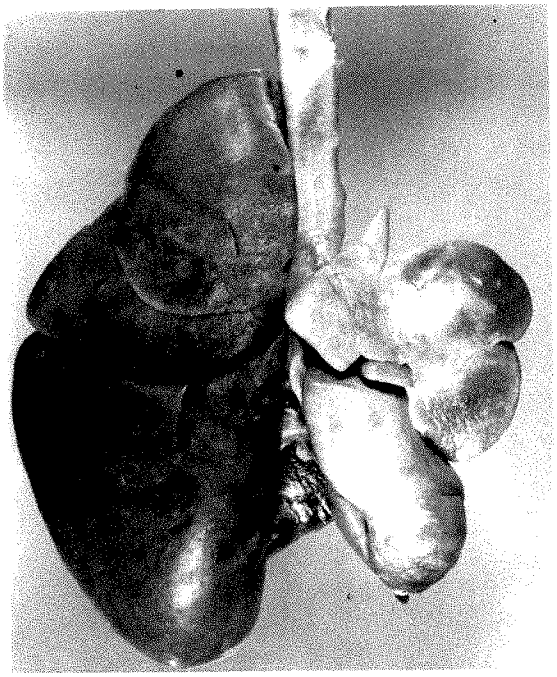

FIG. 9. Gross fixed lungs of Dog 2. Note the shrunken upper, cardiac, and lower (or diaphragmatic) lobes on the right, and the normal left lung. The intermediate lobe can be partially visualized between the lower lobes. This lobe receives blood supply and gas exchange from the right lower lobe and in life is situated between the heart and diaphragm.

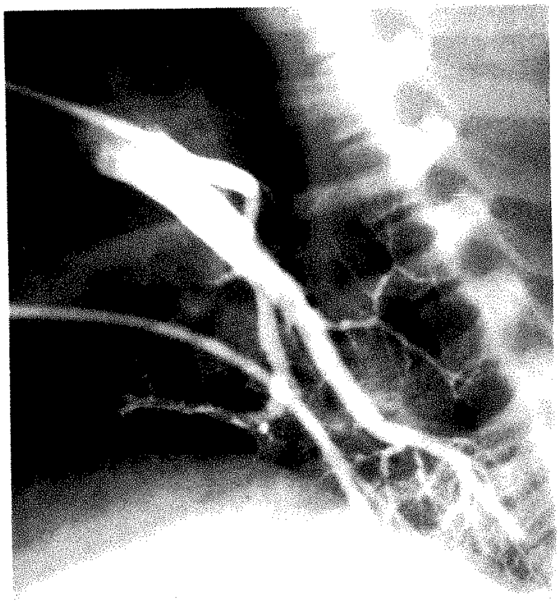

FIG. 10. Pulmonary arteriogram of the right lung in Dog 1, 400 days after irradiation. The vessels are smaller than normal and somewhat irregular. Few lobular arteries can be visualized. The upper lobe artery can be seen twisted caudad, with its origin near the tip of the catheter.

radiation was delivered over 23 to 27 days and the altered function became apparent 5 weeks after the completion of irradiation. The present data show a calculated reduction in blood flow in 2 animals by 52 days and a reduction in all animals by 109 days following a 5 day course of irradiation. The lung scan technique is a more direct and easily performed study and is not influenced by many factors that affect the gas exchange techniques.

The estimation of the distribution of pulmonary blood flow by scanning has been shown to correlate well with the estimated distribution of flow by the classical differential spirometric technique.[8] The photometric measurement of the distribution of the isotope in the lung adds an objective evaluation to what is apparent on viewing the scan. The usual doses of MAA have not had measurable effect on lung function.[5]

The chest roentgenogram is as sensitive as a scan in detecting the onset of radiation pneumonitis in this small series. The scan showed no improvement, however, as

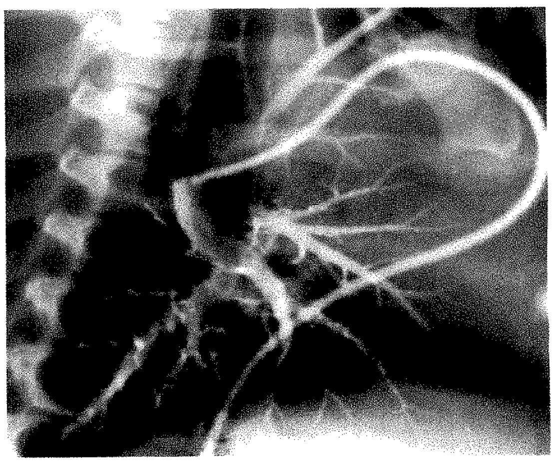

FIG. 11. Pulmonary arteriogram of the left lung in Dog 1, 400 days after irradiation of the right lung. These vessels appear normal except for some displacement accompanying the loss of volume on the right.

the pneumonitis cleared, leaving primarily a loss of volume roentgenographically.

Pulmonary hypertension secondary to radiation injury has not been reported frequently. Freid and Goldberg[4] and later Stone *et al.*[13] noted right ventricle hypertrophy or right heart failure in patients with severe pulmonary reactions. Our own clinical studies showed no evidence of pulmonary hypertension.[1,16] Sweany *et al.*[14] were not able to demonstrate pulmonary hypertension in dogs until at least 6 months following total thoracic irradiation.

The mechanism by which pulmonary blood flow is reduced in the irradiated lung has not been entirely elucidated. It is known that local vasoconstriction affects a reduction in flow in response to anoxia in the lung.[2] This is probably part of the cause of reduced flow in consolidated or atelectatic lung, although other factors such as interstitial or alveolar pressures may be involved. These same factors may play a role in the irradiated lung, but certain anatomic changes have been noted which undoubtedly are important.

Warren and Gates[18] reported that pathologically some pulmonary arteries showed endothelial swelling and vacuolation following irradiation in animals and man. Edema was often marked as well as hyaline swelling of both veins and arteries. Capillary changes were minimal. A recent pathologic study of human material also emphasized fibrous thickening of the intima, growth of elastic fibers in the media, and proliferation of connective tissue in the adventitia of vessels.[9] Using the electron microscope, Phillips[10] studied the irradiated lungs of rats from 1 hour to 12 months after delivering 2,000 r to one hemithorax. The capillary endothelium was sloughed and the endothelial space was replaced by collagen and mast cell infiltrates. Some of the capillaries were recanalized and a functional vessel reappeared. Changes were seen infrequently in the capillaries before 2 months.

Pulmonary arteriograms show the major pulmonary arteries to be patent in the irradiated lungs of the present study, although the caliber was reduced. In 1 dog, the lobular arteries are strikingly absent in some areas, but this may be due at least in part to deficiencies in resolution. Anatomic changes are noted in vessels on microscopic examination, but these alterations are not consistent.

Many factors may contribute to the diminished perfusion of the radiation damaged lung. Vasoconstriction may play a role during the pneumonitis stage. Narrowing or obliteration of arteries, veins, and capillaries must be important later in the sequence. The atelectasis, atrophy, and destruction of architecture noted in some areas obviously affect perfusion.

SUMMARY

Pulmonary blood flow to the irradiated lung in dogs was studied by the lung scan technique.

The flow was markedly reduced by 52 to 109 days following 3,000 r to one lung over 5 days. Perfusion of the irradiated lung decreased as the pneumonitis stage became apparent on chest roentgenograms, and there was no significant improvement in flow as the pneumonitis cleared, leaving the late fibrotic stage.

Mechanisms by which the pulmonary blood flow may be reduced are discussed.

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HODGKIN'S DISEASE: THE NEGATIVE LYMPHOGRAM IN GUIDING RADIOTHERAPY*

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THE radiotherapy of Hodgkin's disease has progressively evolved into an increasingly rational and systematic form of treatment. An understanding of the inverse relationship between the probability of local recurrence and the absorbed radiation dose has clarified the need to adequately irradiate diseased foci.[4,6,11,16,17] A dose of 3,500–4,000 rads delivered in 3–5 weeks is known to reduce local recurrences to a low rate. Another important factor is an awareness that, in many patients, the anatomic spread of Hodgkin's disease is fairly predictable.[14,15] The appreciation of this biologic pattern led Peters[13] to investigate the so-called prophylactic (termed elective in this paper) irradiation of groups of lymph nodes contiguous to the clinically involved areas. This concept is currently being examined prospectively in a number of institutions and a preliminary report has recently suggested that the elective irradiation of clinically normal but adjacent lymph nodes increases the likelihood of patients remaining free of disease following treatment.[7] This understanding of the behavior of Hodgkin's disease and recognition of the need for irradiation with fairly intensive doses provides a reasonable prospect for achieving substantial cure rates in patients with localized disease.

A major contribution to the diagnostic evaluation of the patient with Hodgkin's disease has been the bilateral lower extremity lymphogram. The demonstration of otherwise occult retroperitoneal lymph node involvement is facilitated and staging of the disease is thereby made more accurate. Considerable attention has been devoted to this role of lymphography in the recent literature.[1,10,18,19] In every published series, there is a small group of patients in whom the lymphographic appearance of lymph nodes is suspicious but not diagnostic. This is often because of incomplete opacification and in such cases, inferior venacavography and intravenous pyelography may be of value in reducing the number of indecisive evaluations.

While false positive diagnoses are rare, false negatives occur more frequently since it cannot be anticipated that lymphography will detect microscopic foci of disease. In a few patients, even the retrospective review of well opacified and visualized lymph nodes, subsequently shown to be diseased, fails to reveal any abnormality. This latter group not only demonstrates the importance of follow-up studies but raises the question of treatment policy in patients with negative examinations. The value of follow-up lymphograms after completion of therapy in patients with lymphographic evidence of retroperitoneal lymph node involvement is universally recognized.[2,3,8,9,12] The response to therapy may be seen directly and assessed more accurately than by abdominal palpation or by comparison with contiguous superficial lymph node groups. This is particularly true when chemotherapeutic agents are used because responses of adjacent groups can differ markedly. In addition, recurrence of disease may be detected at an early stage.

The value of post-lymphography roentgenograms in patients with no clinical or roentgenographic evidence of lymph node involvement below the diaphragm has not been so stressed. The failure to appreciate that lymphography is only of relative accuracy may lull the clinician into a false

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sense of security when the opacified lymph nodes are interpreted as normal. This may result in a tendency to dismiss the potential benefit of electively irradiating the infradiaphragmatic lymph nodes. In this communication, a series of patients with negative diagnostic evaluations for paraaortic and pelvic lymph node involvement will be described. Several of these patients have developed active Hodgkin's disease in these sites shortly after receiving radiotherapy to the clinically involved regions above the diaphragm with apparent control of disease in the latter areas.

CLINICAL MATERIAL AND OBSERVATIONS

Between September, 1964, and September, 1966, 60 patients with previously untreated Hodgkin's disease were admitted for evaluation and treatment. The standard diagnostic workup is described in Table I. In 35 of these patients, the disease was clinically limited to the supradiaphragmatic (cervical, axillary, mediastinal, and hilar) lymph nodes with no evidence of systemic or visceral involvement. In each of these 35 patients, physical examination of the abdomen and groins, inferior venacavography, intravenous pyelography, and bilateral lower extremity lymphography were considered within normal limits. As shown in Table II, 11 patients

Table I

PRETREATMENT DIAGNOSTIC EVALUATION

1. Complete history and physical examination
2. Complete blood cell count and urinalysis
3. Posteroanterior and lateral chest roentgenograms (including whole chest tomograms if hilar or massive mediastinal lymph node involvement is present)
4. Inferior venacavography and intravenous pyelography
5. Bilateral lower extremity lymphography
6. Metastatic bone survey
7. Blood urea nitrogen and liver function tests (including liver biopsy if 2 liver function tests are reproducibly abnormal)
8. Bone marrow biopsy

Table II

TREATMENT SCHEMES FOR THE 35 PATIENTS WITH DISEASE CLINICALLY LIMITED TO LYMPH NODES ABOVE THE DIAPHRAGM

No. of Patients	Areas Irradiated			Recurrences Below Diaphragm
	Above Diaphragm	Paraaortic	Pelvic	
7	+	[−]	−	1
11	+	+	[−]	2
17	+	+	[+]	1*

[] Indicates areas where recurrent disease developed.
* Recurrence in an electively irradiated area (2,000 rads/15 days).
Note: One additional patient in the series of 35 has developed biopsy proven Hodgkin's disease in the pelvic lymph nodes which had been electively irradiated with 2,000 r in 12 days since this paper was submitted. As in the other cases, the initially involved sites above the diaphragm were clinically free of disease at the time of recurrence.

received elective irradiation to the paraaortic lymph nodes and 17 patients were electively irradiated to the paraaortic and pelvic lymph nodes. The spleen was also treated in these latter 17 patients. The interval since beginning of treatment ranges from 6 to 30 months. Follow-up roentgenograms were taken routinely at approximately 3 month intervals or more frequently if there was any clinical evidence of disease activity. In addition to posteroanterior and lateral chest roentgenograms, a single anteroposterior roentgenogram of the abdomen was obtained. The position of the patient, centering, film density, and penetration were reproduced as accurately as possible on successive studies.

To the present time, 4 patients have developed definite evidence of active disease in the paraaortic or iliac lymph nodes. In each of these 4 patients, definite radiotherapy had been given to the involved regions above the diaphragm with apparent control of the disease in these sites. The 4 cases are briefly summarized as follows.

REPORT OF CASES

Case I. This 23 year old white male presented with fever, cervical and mediastinal lymph-

adenopathy. Diagnostic evaluation for Hodgkin's disease below the diaphragm was negative and radiotherapy was begun to the cervical, axillary, and mediastinal regions. Four months following completion of treatment, a scout lymphogram of the abdomen demonstrated an increase in size with foamy appearance of the upper paraaortic lymph nodes and displacement of the lymph nodes away from the midline (Fig. 1, *A* and *B*). There was no evidence of recurrent disease above the diaphragm at this time.

Case II. This 30 year old white male presented with fever, night sweats, and cervical and mediastinal lymphadenopathy. Diagnostic evaluation for disease below the diaphragm was negative and radiotherapy was given to the cervical, axillary, mediastinal, and paraaortic regions (the axillary and paraaortic lymph nodes were electively irradiated). At completion of treatment, the patient was asymptomatic. Nine months later, he developed recurrent fever and bilateral iliac lymphadenopathy was palpable. There was no evidence of recurrent disease above the diaphragm at this time and insufficient contrast material remained in the pelvic lymph nodes from prior lymphography for roentgenographic evaluation.

Case III. This 43 year old white female presented with night sweats, generalized pruritus, and cervical and mediastinal lymphadenopathy. Diagnostic evaluation for disease below the diaphragm was negative except for a single suspicious (but not diagnostic) right paraaortic lymph node. Because of this equivocal lymph node, definitive high dose radiotherapy was given to the paraaortic lymph nodes in addition to the cervical and mediastinal lymph nodes. The axillary areas were electively irradiated and the pelvic lymph nodes, completely normal on lymphography, were also electively

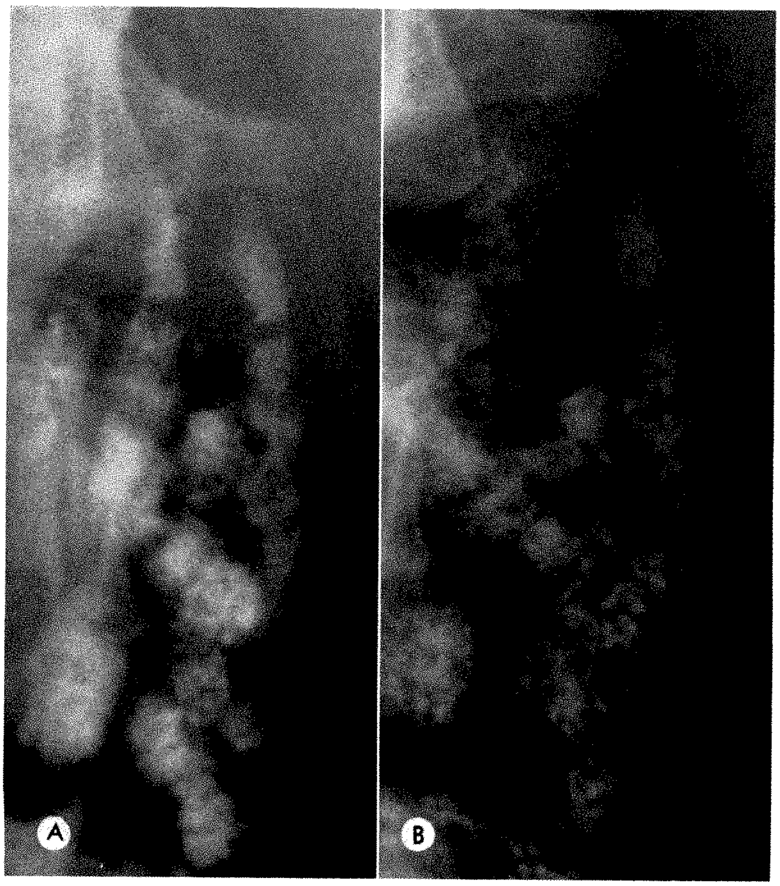

Fig. 1. Case I. (*A*) Normal left paraaortic lymph nodes after lymphography in July, 1964. (*B*) Same region 7 months later showing enlargement and displacement of the lymph nodes.

FIG. 2. Case III. Normal appearance of lymph nodes along left iliac brim immediately after lymphography and a few days before a positive biopsy for Hodgkin's disease was obtained from this group.

irradiated (2,000 rads given in 15 days). Three months after completion of treatment, she was readmitted with fever, nausea, and weight loss. There was no evidence of recurrent disease above the diaphragm. A repeat lymphogram was obtained and interpreted as normal. An exploratory laparotomy was performed and involvement of the liver with Hodgkin's disease was found. No abnormal paraaortic lymph nodes were visualized at operation but a slightly enlarged left common iliac lymph node was biopsied. Histologic examination of this lymph node showed Hodgkin's disease. Review of the second lymphogram obtained several days prior to laparotomy again failed to indicate which lymph node might have been considered suspicious (Fig. 2).

CASE IV. This 17 year old white male presented with left cervical lymphadenopathy and absence of any constitutional symptoms. Diagnostic evaluation for Hodgkin's disease below the diaphragm was negative except for the lymphogram. The original lymphograms were interpreted as equivocal in the right iliac region. Tomograms of these iliac lymph nodes were felt to be normal. Likewise, scout roentgenograms of the abdomen taken 3 and 6 weeks later confirmed the normal appearance of the right iliac lymph nodes. Over a 3 month period, irradiation was given to the cervical, axillary, mediastinal, and paraaortic regions. At the time this treatment was completed, a roentgenogram of the abdomen showed the right iliac lymph nodes to have increased measurably in size and developed a reticular pattern (Fig. 3, *A–C*).

An additional patient of interest was begun on radiotherapy during the period of this review, in whom lymphography performed previously resulted in sufficient contrast material retention to demonstrate the development of retroperitoneal disease on a follow-up roentgenogram of the abdomen 3 years later. The history is summarized as follows.

CASE V. This 66 year old white female was

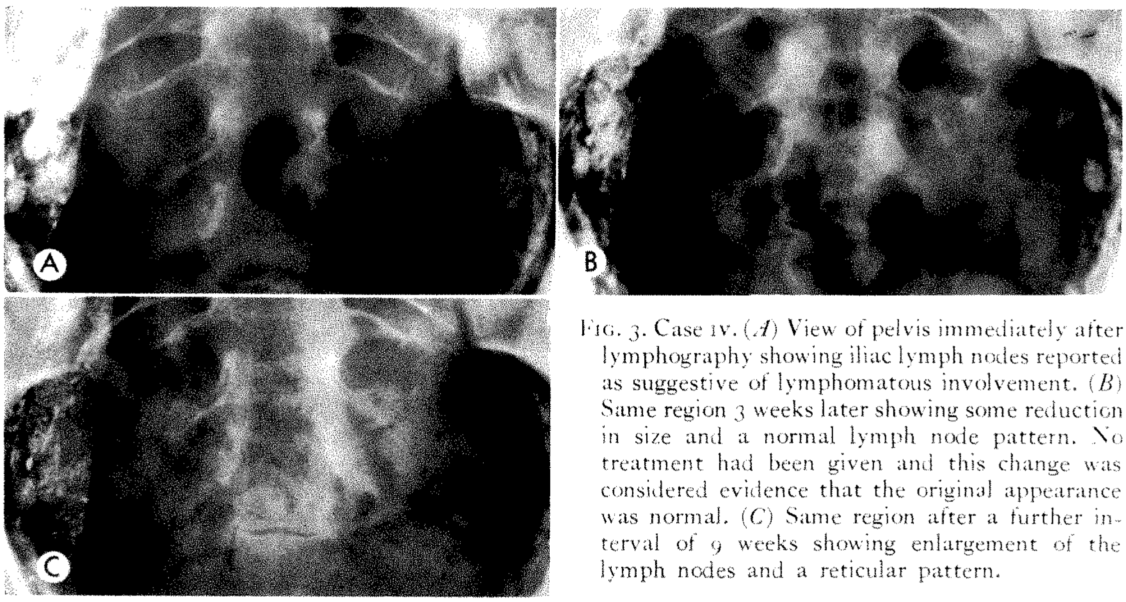

FIG. 3. Case IV. (*A*) View of pelvis immediately after lymphography showing iliac lymph nodes reported as suggestive of lymphomatous involvement. (*B*) Same region 3 weeks later showing some reduction in size and a normal lymph node pattern. No treatment had been given and this change was considered evidence that the original appearance was normal. (*C*) Same region after a further interval of 9 weeks showing enlargement of the lymph nodes and a reticular pattern.

first admitted in 1962 with a history of intermittent swelling of the cervical lymph nodes in the absence of constitutional symptoms. A cervical lymph node biopsy was interpreted as atypical hyperplasia and a bilateral lower extremity lymphogram showed no definite abnormality of the retroperitoneal lymph nodes although there was a suggestion of some spreading of the reticulum. A follow-up lymphogram at 3 months was considered to be normal (Fig. 4*A*). No treatment was given, since at the time of this admission there was no significant palpable lymphadenopathy and the biopsy was nondiagnostic. She was next seen 3 years later, when she presented with generalized palpable lymphadenopathy and anorexia with some weight loss. A repeat lymph node biopsy was unequivocally interpreted as Hodgkin's disease at this time. A roentgenogram of the abdomen showed the lymph nodes with retained contrast medium from 3 years before to have expanded and developed a typical lymphomatous appearance in the paraaortic and pelvic areas (Fig. 4*B*). This was confirmed by inferior venacavography (Fig. 4*C*), pyelography and repeat lymphography (Fig. 4*D*).

DISCUSSION

As reported by others, we have found lymphography extremely useful in the more adequate evaluation and staging of the patients prior to therapy. A further advantage, particularly when extensive lymph node involvement is present, is the aid afforded by the opacified lymph nodes in delineating the required dimensions of the radiation treatment portals. However, when patients with supradiaphragmatic Hodgkin's disease have apparently normal retroperitoneal lymph nodes as shown by lymphography, there may be difficulty in deciding treatment policy. Cases I, II, and III illustrate the false impression which may be created by the normal lower extremity lymphogram. In these 3 patients, it must be assumed that the retroperitoneal lymph nodes were diseased when the lymphogram failed to show any abnormality; and it is possible that with continued follow-up of the group, additional such examples will occur. Active disease developed not only in roentgenographically normal lymph nodes left untreated but, in one instance, in an area irradiated with less than full therapeutic dosages. Further recurrences under the latter conditions will constitute a strong argument for employing full tumoricidal doses for the elective irradiation of potentially involved lymph node groups.

The value of follow-up lymphograms is illustrated by Cases I, IV, and V. A repeat lymphogram in Case IV probably would not have been regarded as diagnostic in itself. Subtle changes are sometimes more easily appreciated in the slightly eluted contrast medium of an earlier examination than in the denser, and inevitably more homogeneous, lymph nodes immediately after a second lymphogram. Likewise, the change in lymph node size as in Case IV may be more significant than either the appearance or absolute measurements at any given time. These are further indications of the limitations of an apparently normal lymphogram. Case V illustrates that, in a few patients, very prolonged follow-up may be possible. The interval here of over 3 years is the longest yet recorded to our knowledge.

As indicated, serial roentgenograms of the abdomen may be critical in the detection of disease extension at a sufficiently early stage to permit control with definitive radiotherapy. When equivocal changes are observed on a follow-up roentgenogram we frequently obtain subsequent roentgenograms at weekly intervals until a definite conclusion is reached. Unfortunately, the rapid elution of contrast material from the lymph nodes in some patients may not allow such serial evaluation for more than a few months. The reasons for the variation in the rate of loss of contrast material from opacified lymph nodes are not understood, but loss of contrast material proceeds rapidly at first. We agree with Fabian *et al.*[2] that after an initial slight increase in size immediately following lymphography, there is a progressive and fairly symmetric disappearance of contrast material with the lymph nodes becoming granular and

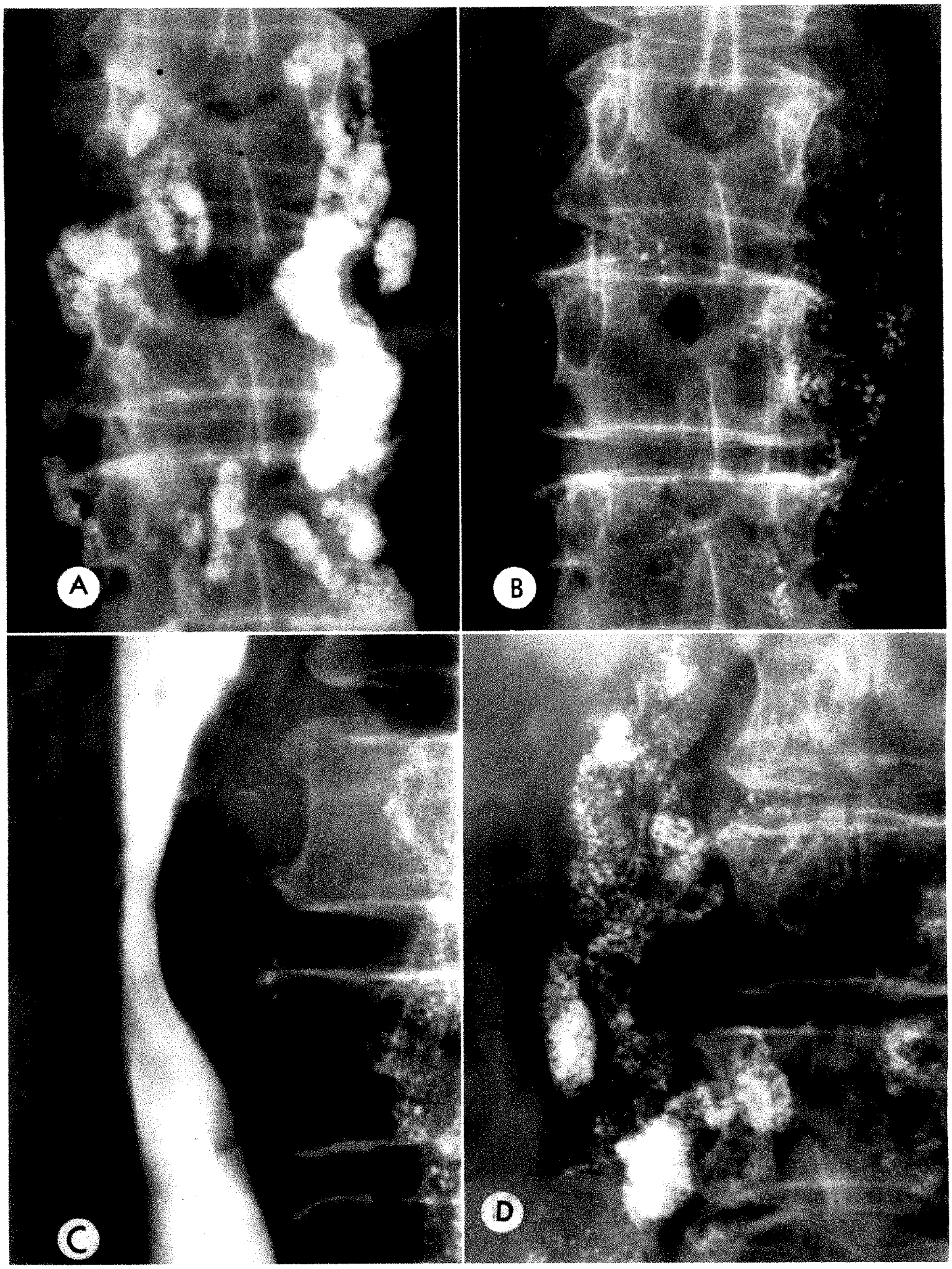

Fig. 4. Case v. (*A*) Normal paraaortic lymph nodes after lymphography in June, 1962. (*B*) Same region 38 months later showing enlargement of the lymph nodes on the left. (*C*) Local view of the inferior venacavogram demonstrating a mass of right paraaortic lymph nodes. (*D*) A second lymphogram the day after *C* confirming the extensive lymphomatous involvement.

gradually smaller in all dimensions. Retention of contrast material in larger lymph nodes, and particularly of extralymphatic droplets, tends to be more prolonged.

Because of elution, the reward from successive follow-up roentgenograms declines but this is difficult to express effectively in percentages. No patient retained sufficient contrast material for all the lymph node groups to be evaluative for 2 years and in most patients, loss of opacification in some lymph nodes occurred within 5–12 months. If adequate retention of contrast material is defined as that amount permitting some type of useful comparison of successive roentgenograms, then nearly all of the patients in this series fall within the definition, even those followed 2 years. One should not expect enough contrast material to be retained to necessarily permit the demonstration of typical lymphomatous appearance when change occurs. Follow-up roentgenograms continue to be useful if the retained opacification shows an increase in lymph node diameter or displacement of opacified lymph nodes by a contiguous, nonopacified structure. A few residual flecks of contrast material, strategically placed, may be diagnostic. For this reason, it may be worthwhile to continue obtaining follow-up roentgenograms for prolonged periods in most patients.

When the frequent situation is encountered, where Hodgkin's disease is apparently confined to regions above the diaphragm and evaluation of the retroperitoneal lymph nodes is negative, several options are available regarding treatment policy. Irradiation of the clinically normal subdiaphragmatic areas may be withheld with reliance placed on serial follow-up studies to demonstrate abnormal changes in the lymphogram. As illustrated by Cases II and III, this may have certain inherent shortcomings. Consideration may also be given to the use of serial lymphograms during the follow-up period or to repetition of lymphography when signs or symptoms of reactive Hodgkin's disease develop.

An alternative approach is the elective irradiation of the paraaortic and pelvic lymph nodes as part of the primary therapy. The rationale for this is similar to the widely accepted use of elective lymph node dissections for a variety of neoplasms by our surgical colleagues. While it is probable that extended elective irradiation is unnecessary for many patients with disease limited to one side of the diaphragm, such treatment has been found well tolerated by patients with more advanced Hodgkin's disease.[5] The value of electively irradiating all major lymph node areas in patients with limited clinical involvement can only be determined by a prospective study employing suitable (less extensively irradiated) controls. Such a clinical trial is currently in progress at our institution.

SUMMARY

Recent experience with patients having Hodgkin's disease and involvement clinically limited to lymph nodes above the diaphragm is presented. These patients had complete diagnostic evaluations including bilateral lower extremity lymphography which was interpreted as normal. Several cases are described to illustrate that some of these patients can be expected to develop active disease in the retroperitoneal lymph nodes and that follow-up roentgenograms of the opacified lymph nodes may not suffice for the detection of this disease progression.

The problem of treatment policy for these patients is discussed.

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THE MICROCIRCULATION OF THE LYMPH NODE*

ITS ROLE IN THE FOURTH CIRCULATION

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IT HAS been known for many years that the thoracic duct and other major lymph trunks empty large quantities of lymphocytes into the blood each day. In man, 35 billion lymphocytes enter the blood daily from the thoracic duct providing a turnover for the blood lymphocytes of several times each day.[1] The origin and fate of these blood lymphocytes has been a mystery. Gowans[3] in 1959 proposed a solution to this mystery, suggesting that most of the blood lymphocytes recirculate into lymph via the lymph nodes and that the lymphocytes repeatedly traverse this circuit during their lifetime. His suggestion was based on the following evidence: (1) The output of lymphocytes from a thoracic duct fistula can only be maintained at its initial level if all the lymphocytes issuing from the fistula are pumped continuously back into the blood; (2) if lymphocytes are not reinfused into the blood, the output of cells from the thoracic duct falls to a low level; (3) when P^{32} or tritiated adenosine labeled lymphocytes are transfused into the blood, a large fraction of their radioactivity can be recovered from the cells in the thoracic duct lymph (90–100 per cent recovery in 5 days); and (4) the number of new small lymphocytes formed each day in the rat amounts to only a small fraction of the normal daily output from the thoracic duct.

In 1964, Gowans and Knight[4] and Marchesi and Gowans,[5] utilizing tritium labeling techniques and electron microscopy, demonstrated the passage of lymphocytes from the blood through the specialized postcapillary venule of the lymph node. This demonstration identified one of the crucial pathways in the circulation of lymphocytes.

It is now well established that there is a large-scale circulation of the lymphocytes, which Yoffey[8] has dubbed the fourth circulation, likening it to that of blood, lymph, and cerebrospinal fluid. The lymphocytes enter the blood from the main lymphatic trunks, pass to the lymph nodes via the specialized postcapillary venules and reenter the lymph sinuses in the nodes. The specialized postcapillary venules are found exclusively in lymphocytic tissues; *e.g.* lymph nodes, tonsils, spleen, and Peyer's patches. Schulze[7] described their unique features which consist of an unusually tall or cuboidal endothelium and the presence of lymphocytes within the walls of the vessel.

We have studied the microcirculation of the lymph node by the technique of microradiography, complemented by histology. This report deals with one aspect of that study, the position of the postcapillary venule in the microcirculation of the lymph node. The significance of the fourth circulation to oncology will also be discussed.

MATERIAL AND METHOD

To visualize the pattern of the blood circulation in adequate detail and yet in a sufficient thickness of tissue, microradiography was used. The first step, therefore, has been to perfuse the vascular system with radiopaque media.

An apparently healthy, 7 kg. female mongrel dog was anesthetized with intravenous pentothal. Two PE 240 catheters

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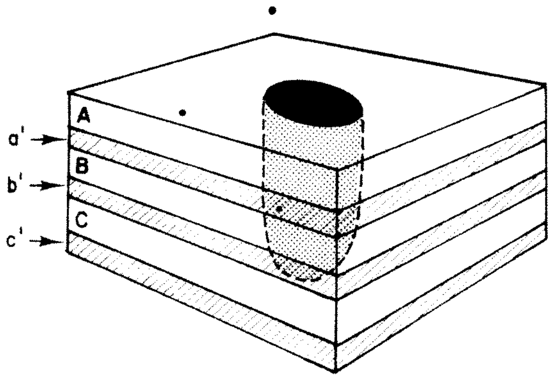

FIG. 1. Diagram of alternate sections of lymph node. A, B, C = 80 micron sections for microradiography. a', b', c' = 8 micron sections for histology.

were passed via the femoral arteries to the level of the abdominal aorta. Two similar catheters were passed into the inferior vena cava via the femoral veins.

After the intravenous administration of 50 mg. heparin, 30 per cent colloidal barium sulfate, wt./vol. (micropaque), was injected via the femoral arteries. The venous return became slightly milky white almost immediately. Perfusion pressure was 140 mm. Hg. Two liters of perfusate was injected at which time the venous return ceased.

The organs were removed post mortem and fixed in 10 per cent formalin. The lymph nodes were then dehydrated, cleared, and embedded in paraffin wax. The right and left popliteal node and cervical node were chosen for study, using alternate serial sections (Fig. 1). The amount of material wasted between each section is shown in Table 1. The 80 micron sections were used for microradiography, and the 8 micron sections were stained with hematoxylin and eosin for standard histologic studies.

TABLE I

SERIAL SECTIONS: ALTERNATE HISTOLOGY SECTIONS 8 MICRONS EACH AND MICRORADIOGRAPHY SECTIONS 80 MICRONS EACH

Serial Section No.	Waste after Histology Section (microns)	Waste after Microradiography Section (microns)
1	40	28
2	38	48
3	30	16
4	36	24
5	56	24
6	38	8
7	34	48
8	28	24
9	20	18
10	26	8

Microradiography was done with a Picker "Hot-Shot" portable x-ray unit with a beryllium window. Sections were placed in contact with Kodak high-resolution glass plates. The factors used were: 12 kv., 10 ma., 8 minutes, 15 cm. film-to-target distance.

The final step was to take Polaroid pictures of the microradiographs and of the histology slides. PolaPan Type 52 films were used in a standard Polaroid camera attachment to our microscope.

Examples of the pictures are seen in Figure 2 (histology) and Figure 3 (microradiography).

RESULTS

The vessels were adequately filled both on the microradiographs and on the histology slides; there was no evidence of extravasation of the contrast medium. From the photographs of both sets of sections the course of the major arterial and venous vessels was traced; however, the

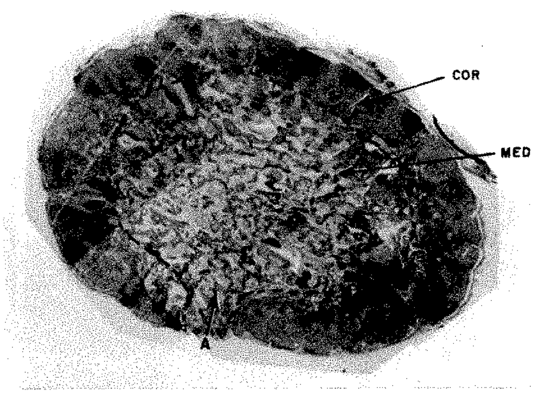

FIG. 2. Cross section of dog popliteal lymph node. (H & E ×21, 8μ.) COR = cortex; MED = medulla; A = region where medulla extends almost to capsule.

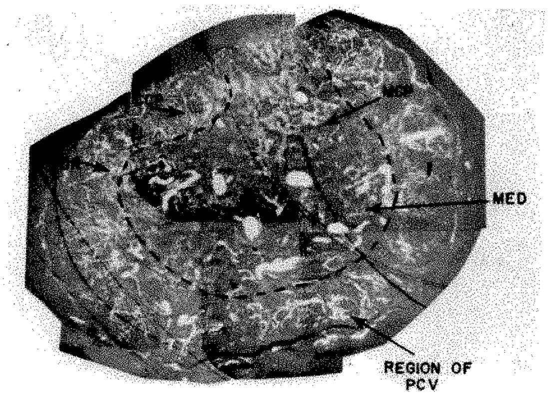

Fig. 3. Microradiograph of cross section adjacent to Figure 2. (×21, 80μ.) COR = cortex; MED = medulla; CCP = cortical capillary plexus; MCP = medullary cord capillary plexus (extending to the capsule); REGION OF PCV = region of postcapillary venules.

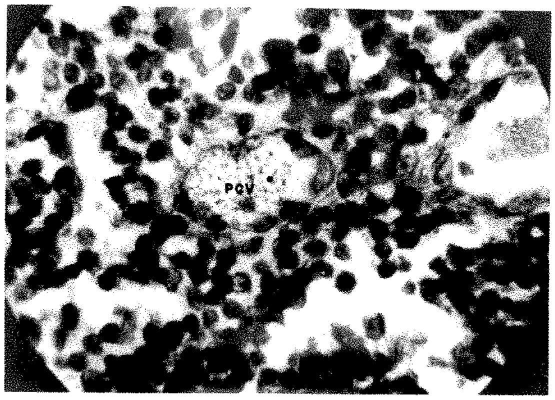

Fig. 5. Postcapillary venule (PCV) in cortex. Note cuboidal-like endothelium. (H & E ×600, 8μ.)

filling of the major veins was incomplete, due to a technical defect. The position of major vessels in both types of preparations was correlated by identifying the vessel histologically and then locating on the corresponding microradiograph a similar vessel in the same position and of a similar diameter.

From a review of the serial sections, an over-all pattern of vessel distribution was observed. The cortical blood supply consists of a few small arteries with numerous capillary vessels and a series of corticomedullary veins. The medulla is supplied by a few arteries, has numerous capillaries intertwined as a plexus in the medullary cords, and is drained by multiple, wide veins (Fig. 3).

The postcapillary venules were identified on the histologic sections on the basis of: (a) their position in the subcortex and at the corticomedullary junction; (b) the prominent cuboidal epithelium; and (c) the presence of lymphocytes within the wall of several of these vessels (Fig. 4–8). The postcapillary venules were seen to be well filled with contrast medium (Fig. 4–8). The corresponding areas of the microradiographs were photographed to identify these postcapillary vessels (Fig. 9; and 10).

The postcapillary venules were more difficult to locate on the microradiographs; but on the basis of corticomedullary location in the specimen and the rela-

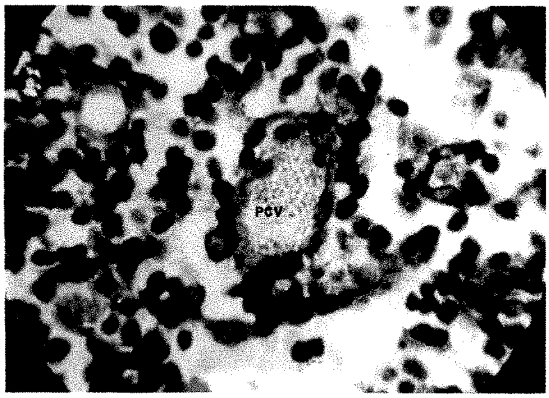

Fig. 4. Histologic section demonstrating a postcapillary venule (PCV) filled with contrast medium. (H & E ×600, 8μ.)

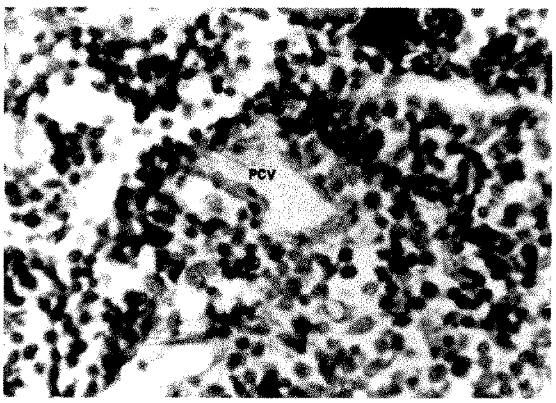

Fig. 6. PCV = postcapillary venule in subcortical region. (H & E ×400, 8μ.)

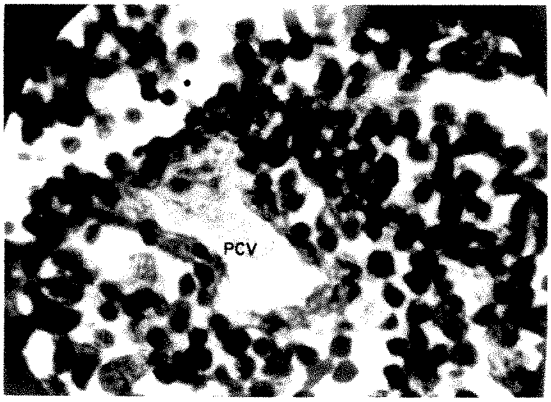

Fig. 7. Same vessel as in Figure 6. Lymphocytes surround the vessel. (H & E ×600, 8μ.)

Fig. 9. Microradiograph of corticomedullary junction of lymph node. PCV = postcapillary venule; C = capillary; V = vein. (×100, 80μ.)

tion to capillaries, arteries, and veins, the vessels could be identified with a fair degree of certainty. In the present study, the thickness of the microradiographic sections plus the thickness of waste material between the sections did not allow exact identification of the vessels in the corresponding histologic sections. However, the alternate sections did correlate sufficiently to demonstrate that the postcapillary venules were not in direct contact with germinal centers, medullary cords, or the reticulated medullary capillary plexus.

The postcapillary venules were shown, on the microradiographs, to pass radially from the site of confluence of the cortical capillaries to the large veins at the corticomedullary junction. These large veins were arranged, in a section of the lymph node in an elliptic pattern at the corticomedullary junction. The postcapillary venules traverse the cortex in a direction from the surface into the depths to join these draining veins.

There were several observations noted concerning the capillary vessels. In Figure 3, the submarginal and dense cortical lymphatic tissue capillary plexuses are seen to consist of relatively straight vessels while the capillary plexus of the medullary cords consists of more intertwined, less linear vessels. Figure 11 is a microradiograph of the medullary capillary plexus which gives a honeycombed appearance. At higher magnification (Fig. 12) the plexu

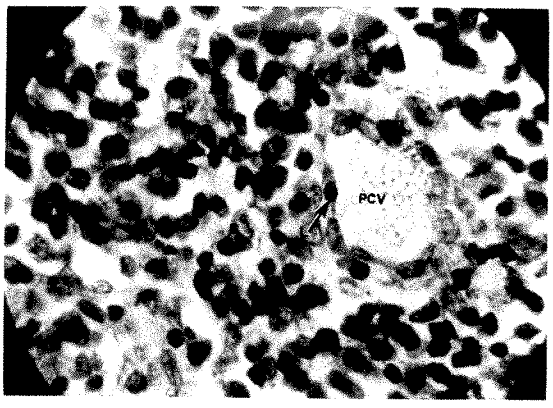

Fig. 8. PCV = postcapillary venule; L = lymphocyte in endothelial wall. (H & E ×600, 8μ.)

Fig. 10. Microradiograph of corticomedullary junction. PCV = postcapillary venule; C = capillary; V = vein. (×100, 80μ.)

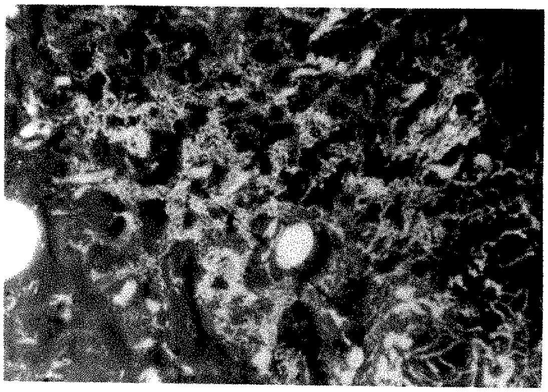

Fig. 11. Microradiograph of medullary region of lymph node. The honeycombed capillary plexus network is situated in the medullary cords. (×35, 80μ.) See Figures 12, 13 and 14.

is seen to consist of very fine, extremely intertwined vessels of capillary dimensions. The clear spaces surrounded by this plexus of vessels are found to correspond to the lymph sinuses when their position is correlated with adjacent histology sections (Fig. 13; and 14).

There is a paucity of obvious connections between the cortical and medullary vasculature, and less small vessel supply to the germinal centers than to the remainder of the cortical lymphatic tissue or medullary cords.

DISCUSSION

The electron photomicrographs of

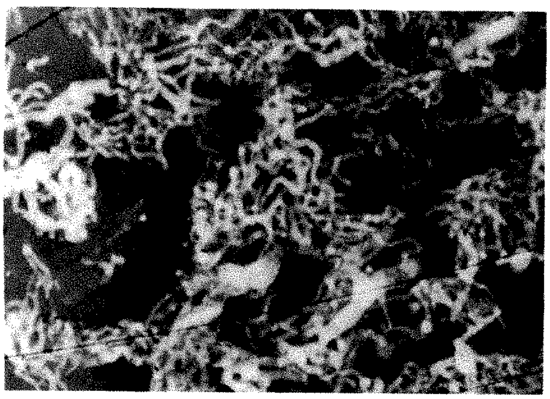

Fig. 12. Microradiograph of medullary region with greater magnification. The fine vessels are capillaries. The intervening dark spaces are occupied by the medullary lymph sinuses. (×100, 80μ.)

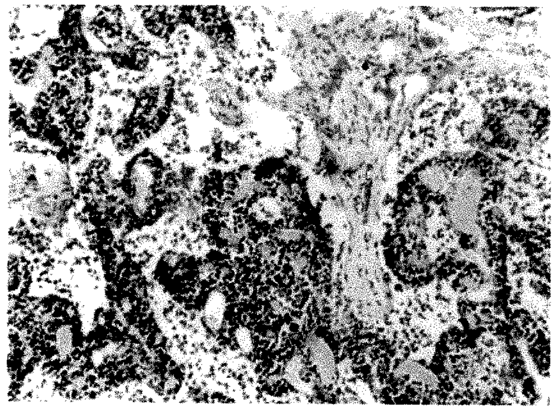

Fig. 13. Histologic section of medullary region of lymph node. Section is adjacent to that of microradiographs of Figures 11 and 12. Medullary cords consist of capillaries filled with contrast medium surrounded by packs of lymphocytes. The clear channels containing loose cells are the lymph sinuses. (H & E ×100, 8μ.)

Marchesi and Gowans[5] demonstrate the unique morphology of the postcapillary venule as well as its role in the fourth circulation (Fig. 15; and 16).

Figure 15 is an electron photomicrograph (magnification ×6,000) of a postcapillary venule in a rat lymph node, showing the cuboidal endothelial cells projecting into the lumen and lymphocytes

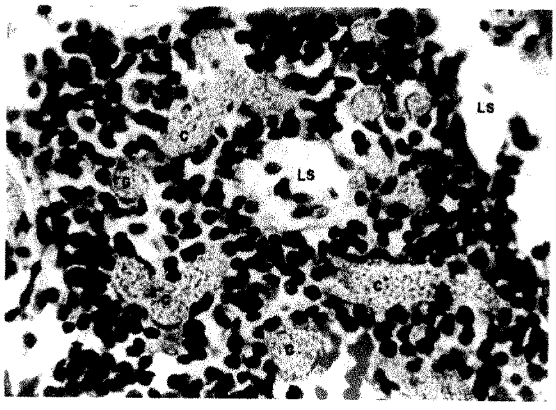

Fig. 14. Histologic section of medullary region with higher magnification. C=capillaries (filled with perfused contrast medium); LS=lymph sinuses. The endothelial cells of these capillaries are typically flat and should be contrasted to the cuboidal endothelium of the postcapillary venules (Fig. 4–8). The lymphocytes are a cushion between the lymph sinuses and capillaries. (H & E ×400, 8μ.)

Fig. 15. An electron microscope view of a postcapillary venule. The endothelial cells are tall and project well into the lumen. Lymphocytes are in the endothelial cell cytoplasm; others are situated about the basement membrane. (From Marchesi and Gowans.[5]) En = endothelial cell nucleus; L = lymphocyte nucleus; R = red blood cells (Mag. ×6,000).

within the endothelial cell cytoplasm and near the basement membrane of the vessel. Note the pseudopod lymphocyte at the lower left, presumably passing from blood vessel to cortex of lymph node. Other lymphocytes appear to be in various phases of migration through the postcapillary venule. Figure 16 shows the migration diagrammatically and compares a lymphocyte migrating directly *through* the endothelial cell with a polymorphonuclear leukocyte migrating *between* the endothelial cells of the venule.

Our microradiographs show that the postcapillary venule receives blood exclusively from the cortex of the lymph node and not from the medulla. The medullary capillaries are in close contact with the lymph sinuses, but the blood from these sites does not pass into the postcapillary venules.

Burwell[2] carried out vascular studies in the rabbit lymph node using India ink as a perfusion medium. He found subcapsular capillary loops, the apogee of which was in close relationship to the marginal sinuses of the lymph node. Burwell pointed out that contact between the lymph node and pre-postcapillary venule blood could fit in with other evidence that antigens carried to the node by lymph might attract sensitized lymphocytes into the node. Our microradiographs did not show these subcapsular capillary loops, possibly due to the technical deficiency of failure to fill completely the larger veins. Otherwise, our findings are similar to those of Burwell.[2]

The fourth circulation, that is, the circulation of lymphocytes, has implications in the pathology of neoplasms, particularly chronic lymphatic leukemia. It is difficult to imagine how chronic lymphatic leukemia could manifest itself in any form other than that of dissemination into all of the lymphocytic tissues, even if it began as a localized process. Assuming an active circulation of chronic lymphatic leukemia cells, local irradiation to an enlarged spleen ought to reduce the entire leukemic cell population, resulting in regression not only of splenomegaly but of lymphadenopathy as well. This abscopal effect is often observed.

Radiation effects on normal lymphocytic tissues ought to be influenced by the fourth circulation. Cell depletion measurements[6] of lymph nodes after equal doses of local *versus* whole body irradiation ought to show less depletion in the locally irradiated lymph node because of repopulation by migrating lymphocytes.

SUMMARY AND CONCLUSIONS

1. The fourth circulation is that of the lymphocytes, which circulate from lymph to blood to lymph node and back to lymph. The specialized postcapillary venule is the pathway from the blood to the lymph node in this circuit.

2. Microradiography is a useful method to show the position of the postcapillary venule in the microcirculation of the lymph node. Postcapillary venules apparently drain blood from the cortex of the lymph node, but not from the medulla. The cortical blood vessels are mainly in the dense

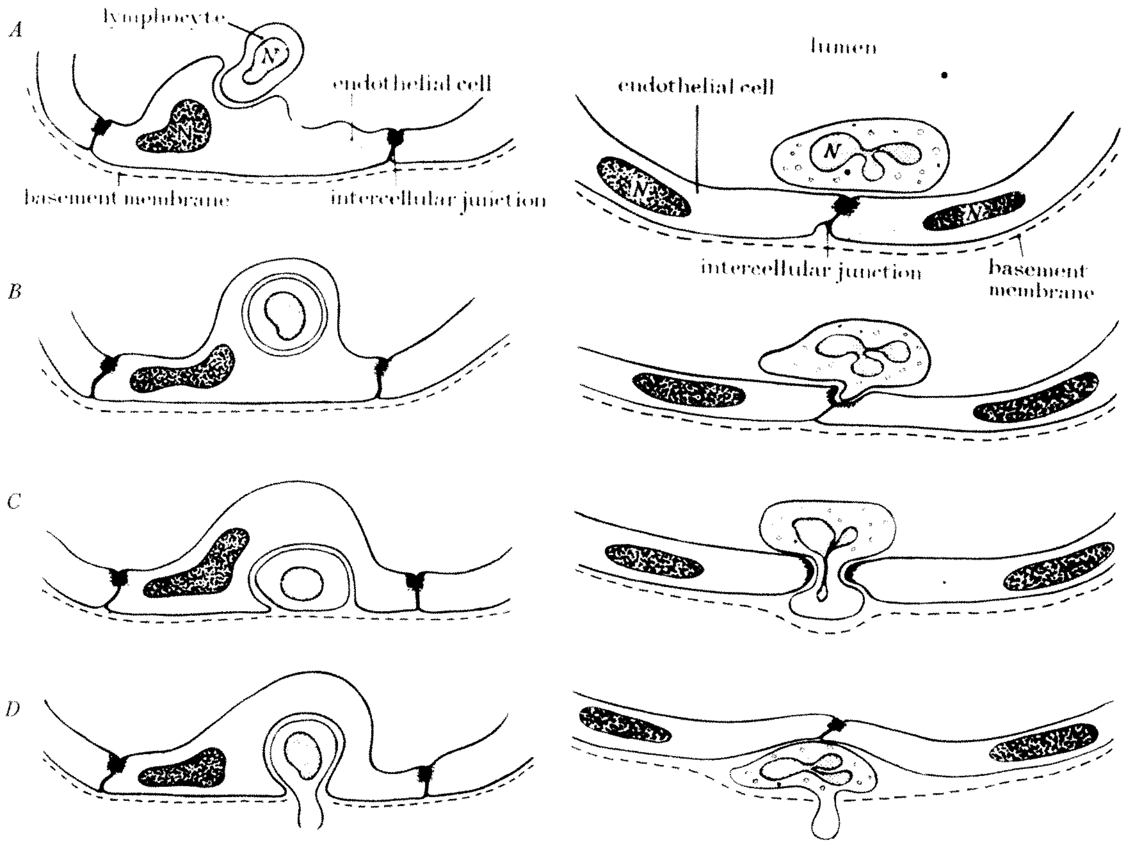

FIG. 16. Diagrams of mode of migration of lymphocytes on left and polymorphonuclear leukocytes on right through the endothelial wall of venule. The lymphocyte passes *through* the endothelial cell, while the polymorphonuclear leukocyte passes *between* the endothelial cells. (From Marchesi and Gowans.[5])

aggregates of lymphocytes; a comparatively scant blood supply is seen in the germinal centers. The significance of these anatomic findings depends on physiologic studies of lymphocytes and the lymph node.

3. Lymphomas, particularly chronic lymphatic leukemia, might very well disseminate through the lymphocytic tissues by entering the fourth circulation.

4. Radiation effects on normal lymphocytic tissues and lymphomas must be influenced by lymphocyte circulation. A locally irradiated lymph node ought to be repopulated more rapidly than after whole body irradiation. Local irradiation of the spleen in chronic lymphocytic leukemia will reduce the entire circulating lymphocyte population, thereby producing regression not only of splenomegaly but of lymphadenopathy as well.

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SKELETAL SCINTIGRAPHY AS AN AID IN PRACTICAL ROENTGENOGRAPHIC DIAGNOSIS*.

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ROENTGENOGRAPHIC findings of skeletal diseases often appear late. Clinical symptoms precede them by weeks or even months. Changes of the macrostructure of bone, which can be evaluated on roentgenograms, are the result of local or generalized alterations of calcium turnover of the bone. Early information about this function can be obtained by examination with radioisotopes.[1] As skeletal scintigraphy provides an image of the anatomotopographic distribution and extension of pathologic bone processes, this procedure is of special interest to the radiologist.

With the purpose of investigating the diagnostic value of bone scintigraphy, the scintigrams of 200 patients with various bone diseases were compared with their roentgenograms. The following report will summarize some of our observations.

TECHNIQUE

The technique of skeletal scintigraphy consists of the application of a radioactive bone seeker, followed by external registration and measurement of the radioactivity in the bones with a conventional scanner. As strontium ions are incorporated into the bone tissue in the same way as calcium ions, most authors use strontium 85; it is inexpensive and can be measured by conventional scanning devices.[2–12] The skeletal scintigrams are taken 3 to 7 days after the intravenous injection of 50 μc of the isotope.

RESULTS

Skeletal scintigrams of normal adults show a slight amount of radioactivity in the vertebral column, in the iliosacral region, and in the joints of the extremities, especially in the weightbearing hip, knee and ankle joints. Radioactivity visualized on scintigraphy in other locations usually represents a pathologic condition.

Figure 1, *A–C* illustrates the roentgenograms and scintigrams of 3 different patients. The scintigraphic images were similar. Increased radioactivity of comparable size and intensity was detected in one vertebral body. The first patient, a 65 year old man, had trauma to his back 4 weeks previously with a fracture of the fourth lumbar vertebral body. The second patient, a 53 year old man, had an involvement of the third lumbar vertebra by Paget's disease. The first lumbar vertebra of the third patient, a 49 year old woman, was eroded by metastases from a mammary carcinoma.

The findings in these 3 patients demonstrate the nonspecificity of a positive scintigram. Different causes can lead to an increase of the calcium accretion rate, and create a condition in which radioactivity is accumulated and visualized by scintigraphy. The differential diagnosis of a skeletal lesion can be made only by roentgenography. However, scintigraphy, which provides quantitative information, determined by the count rates, gives an indication of the activity of a pathologic bone process.

A 58 year old man had a bicycle accident 2 weeks before the examination and complained of backache. Roentgenologically, a wedge deformity of the second lumbar vertebral body with indentation of the superior vertebral plate was observed (Fig. 2, *A* and *B*). The negative scintigraphic findings prove that no reactive bone formation was present. The fracture, therefore, was old and healed. This de-

* Presented at the "Russell Morgan Day" of the Rocky Mountain Radiological Society Annual Meeting, Denver, Colorado, August 18, 1967.
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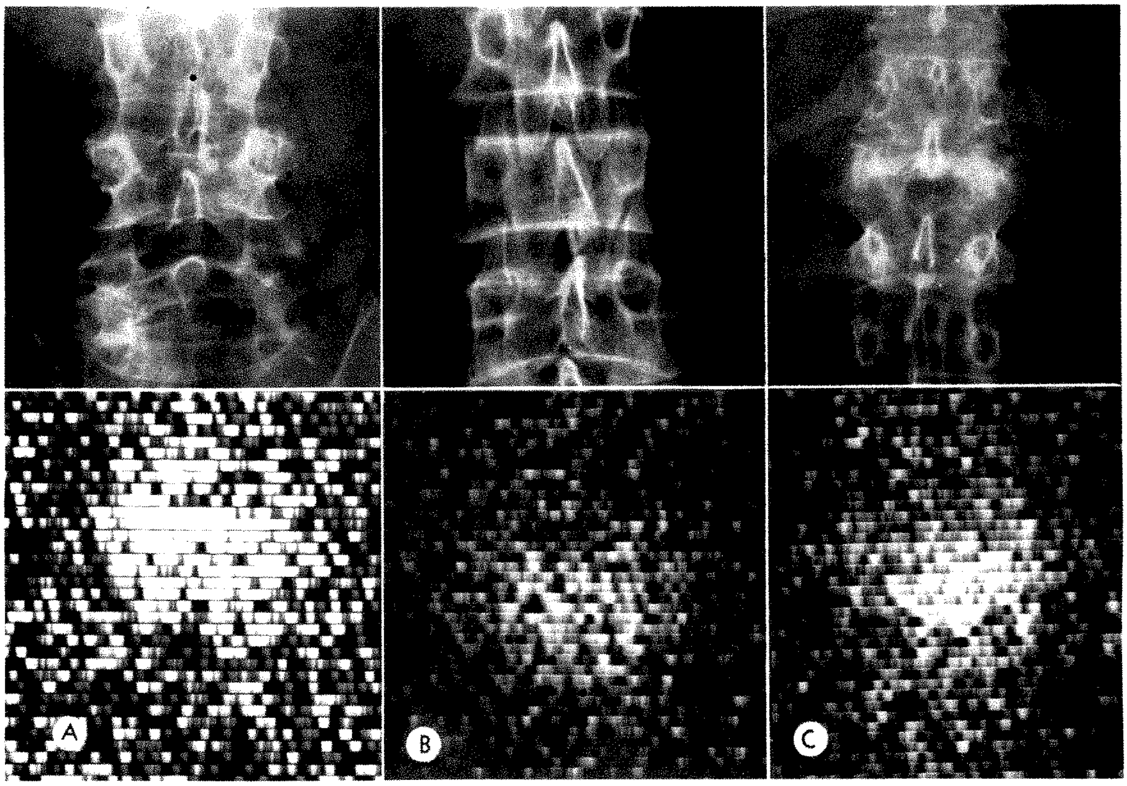


Fig. 1. Similar scintigraphic findings caused by 3 different pathologic lesions. (*A*) Fracture of the fourth lumbar vertebra in a 65 year old man. (*B*) Paget's disease of the third lumbar vertebra in a 53 year old man. (*C*) Metastasis to the first lumbar vertebra from a primary carcinoma of the breast in a 49 year old woman

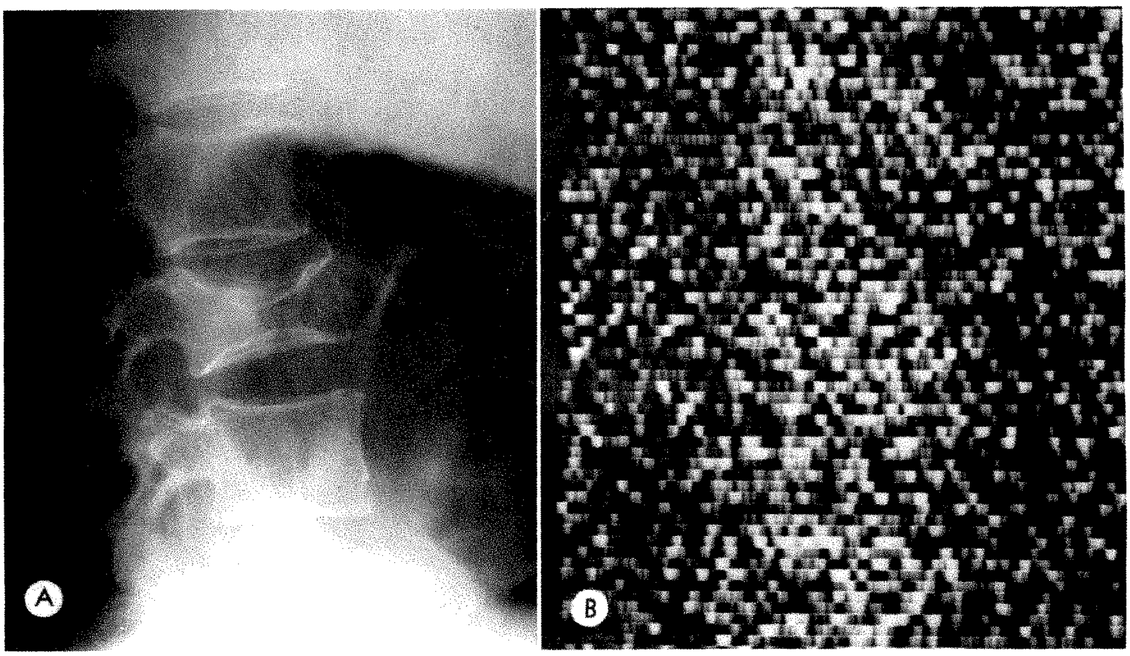


Fig. 2. (*A*) Old healed fracture of the second lumbar vertebra in a 58 year old man. (*B*) Scintigraphically, no increase of radioactivity at the fracture site is demonstrated.

formity was unrelated to the recent trauma.

Scintigraphic experience on patients with vertebral fractures indicates that the measured uptake of radiostrontium is in direct relationship to the activity of the healing process. The highest count rates can be noted about 1 month after the occurrence of the fracture. Later, the activity slowly decreases and reaches a normal value 2 years or more after the trauma (Fig. 3). A permanent slight increase of the count rate can be noted when secondary degenerative changes develop in the vicinity of the fracture site.

Fractures of the base of the skull, upper thoracic spine, sternum and sacrum are roentgenographically often difficult to demonstrate. Skeletal scintigraphy can be of help for the detection of these hidden fractures.

A 34 year old man fell from a roof 16 feet high. Roentgenologically, multiple fractures of the ribs and one scapula were present. On the scintigram of the thoracic region, examination of the eighth and ninth right ribs disclosed circumscribed areas of markedly increased radioactivity. Unexpectedly a similar radioactive zone could be observed in the region of the second, third and fourth thoracic vertebrae (Fig. 4, *A* and *B*). The roentgenographic examination failed to show an abnormality at this level. The laminagraphic examination, however (Fig. 5), confirmed the scintigraphic findings demonstrating fractures of the respective thoracic vertebrae.

When the healing process of a fracture is complicated by inflammation or by the development of pseudoarthrosis, the count rates at the fracture site reach abnormally high levels, and show no tendency to return to normal.

A 59 year old patient was treated with hip arthrodeses combined with intertrochanteric osteotomy for severe degenerative disease 5 months previously. The clinical and roentgenographic findings caused one to be suspicious of a pseudoarthrosis at the osteotomy site and of nonunion of the hip arthrodeses (Fig. 6, *A* and

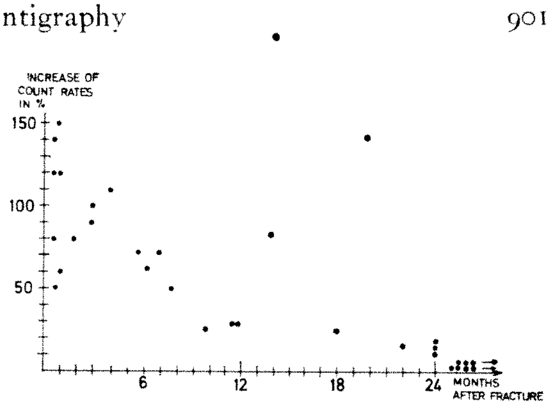


Fig. 3. Comparison between increase of count rates and fracture age in 30 vertebral fractures.

B). Scintigraphy showed a high increase of the radioactivity in the left hip and intertrochanteric region with count rates 10 times above normal, corroborating the clinical and roentgenographic impressions. In this patient a rearthrodesis with osteosynthesis of the femoral shaft to the pelvis was undertaken.

Our experience based on the study of 35 patients who had been subjected to various surgical hip procedures proves that abnormally high radioactivity at the operative site is a sign of infection or of unstable fixation and indicates the need for special treatment, bed rest and/or reoperation.

The visualization of bone tumors or metastases on a scintigram depends on the presence of a reactive bone process with an increased accretion rate in the surrounding bone. Osteoblastic as well as osteolytic bone lesions can be detected and outlined by skeletal scintigraphy.[2–12] Usually, the amount of radioactivity on the scintigram is directly related to the activity of the neoplastic lesion. Benign bone tumors with slow-growing tendencies and inactive metastases often are scintigraphically negative. Wherever there is active tumor growth the scintigraphic findings are positive. This may be seen in malignant and nonmalignant neoplasms.

A cystic lesion with calcification in its proximal portion was observed in the distal femur of a 61 year old patient (Fig. 7, *A–C*). Roentgenologically, the diagnosis of an enchondroma was made, and later proved by biopsy. In the expanding por-

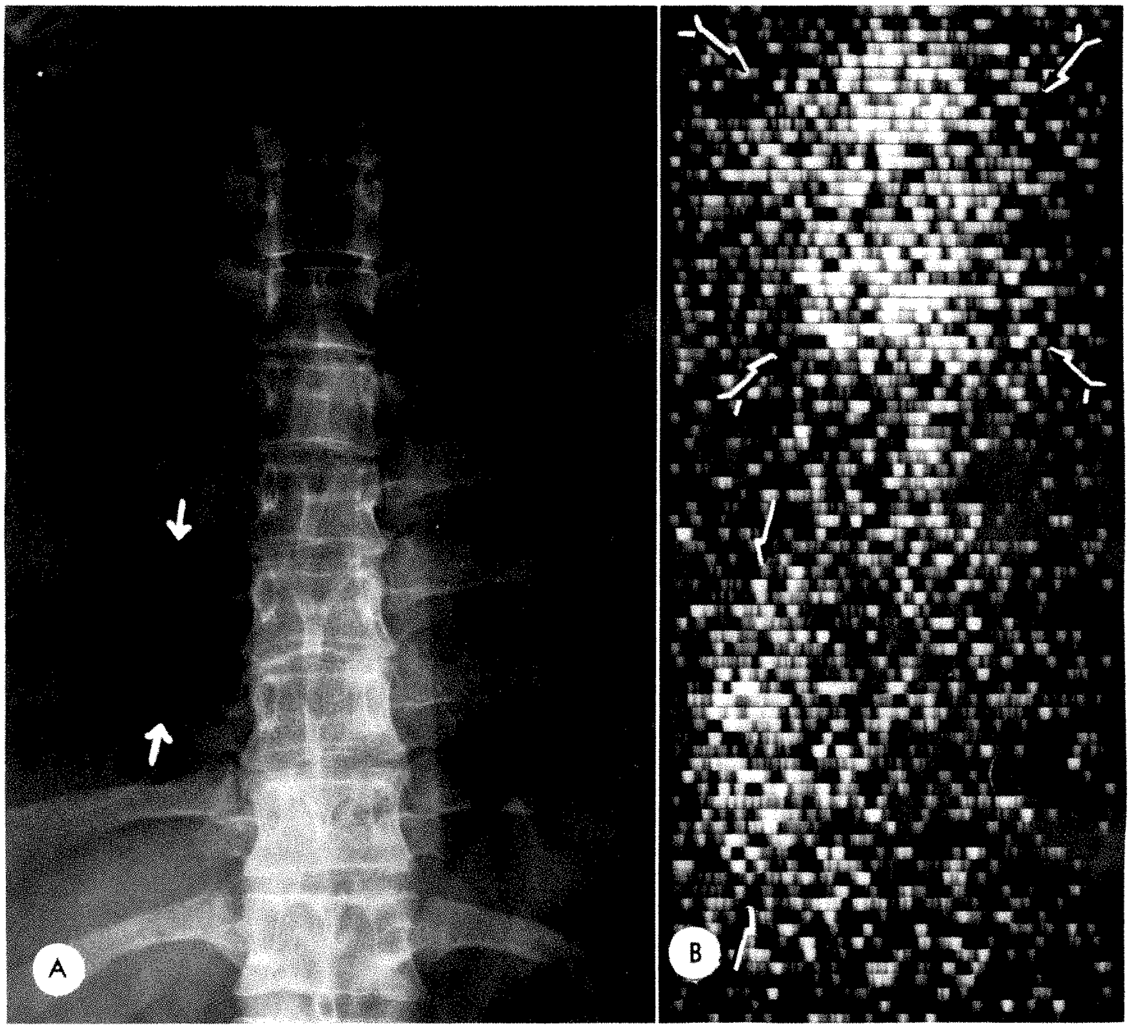


Fig. 4. (*A*) Fractures of the eighth and ninth ribs in a 34 year old man. (*B*) Increased radioactivity at the site of the rib fractures ↑ and in the upper thoracic spine ↑, where on the roentgenogram no fracture is demonstrated. (Reproduced with permission from *Fortschr. a. d. Geb. d. Röntgenstrahlen u. d. Nuklearmedizin*, 1967, *107*, 654.)

tion of the lesion, circumscribed increased radioactivity was present as a sign of reactive bone formation secondary to active tumor proliferation. However, in the proximal calcified portion of the tumor, the scintigraphic findings were negative indicating tumor inactivity. The arteriogram showed no difference in the gross blood supply of these two portions of the lesion.

Tumor inactivation following radiotherapy was demonstrated in a 44 year old patient (Fig. 8, *A* and *B*). Two years previously an osteolytic metastasis from a mammary carcinoma in the left iliac bone was irradiated using Co^{60} teletherapy. Because the patient was complaining again of pain in the left hip, roentgenographic studies and skeletal scintigraphy were performed. The irradiated metastasis appeared scintigraphically inactive. A new osteolytic metastatic lesion in the trochanteric region, however, was highly radioactive. On the roentgenogram the lesion was only faintly visible. Following selective irradiation of the left hip the pain disappeared.

Early skeletal metastases can be recognized by scintigraphy, even in cases with negative roentgenographic findings.[1–12] This observation has been confirmed by our own investigations. As degenerative, inflammatory, traumatic and dystrophic bone diseases may disclose positive scintigraphic findings, it is often unwise to suggest the diagnosis of early metastasis without roentgenographic confirmation. For the differential diagnosis of such cases the results of blood chemistry should also be taken into consideration.

A 70 year old man suspected clinically of having vertebral metastases from an unknown primary tumor showed on the roentgenograms and laminagrams of the thoracic spine moderate degenerative changes and diffuse osteoporosis; there were no signs of metastases (Fig. 9, *A* and *B*). On the scintigram the radioactivity of the spine appeared particularly increased in the lower thoracic region. This could be a consequence of the osteoporosis and osteoarthritis, as well as a sign of early metastases. As the alkaline phosphatase was

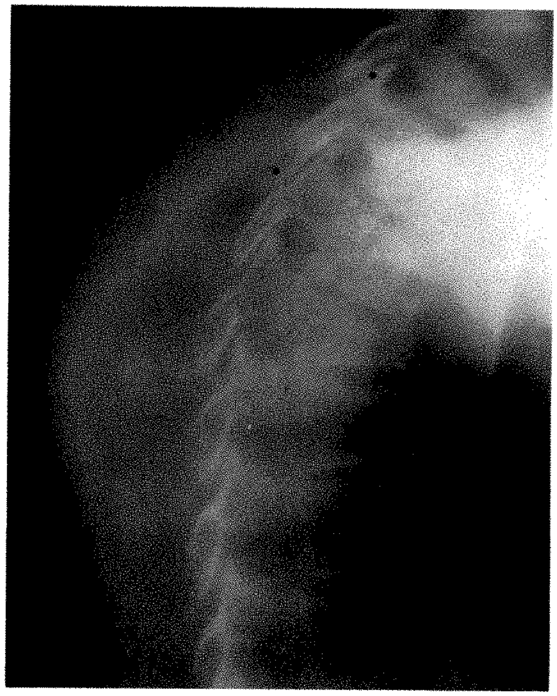


FIG. 5. Same patient as in Figure 4, *A* and *B*. The laminagram reveals fractures of the second, third and fourth thoracic vertebrae. (Reproduced with permission from *Fortschr. a. d. Geb. d. Röntgenstrahlen u. d. Nuklearmedizin*, 1967, *107*, 654.)

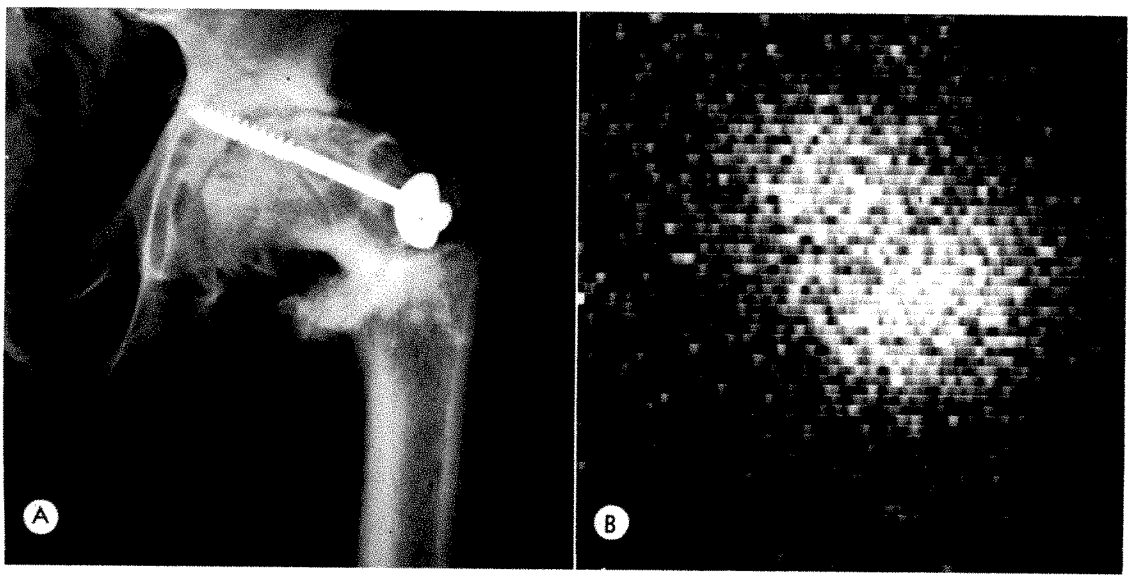


FIG. 6. (*A*) Hip arthrodesis and intertrochanteric osteotomy for degenerative joint disease 5 months previously in a 59 year old man. (*B*) Increased radioactivity at the site of the arthrodesis and osteotomy due to nonunion. (Reproduced with permission from *Fortschr. a. d. Geb. d. Röntgenstrahlen u. d. Nuklearmedizin*, 1967, *107*, 654.)

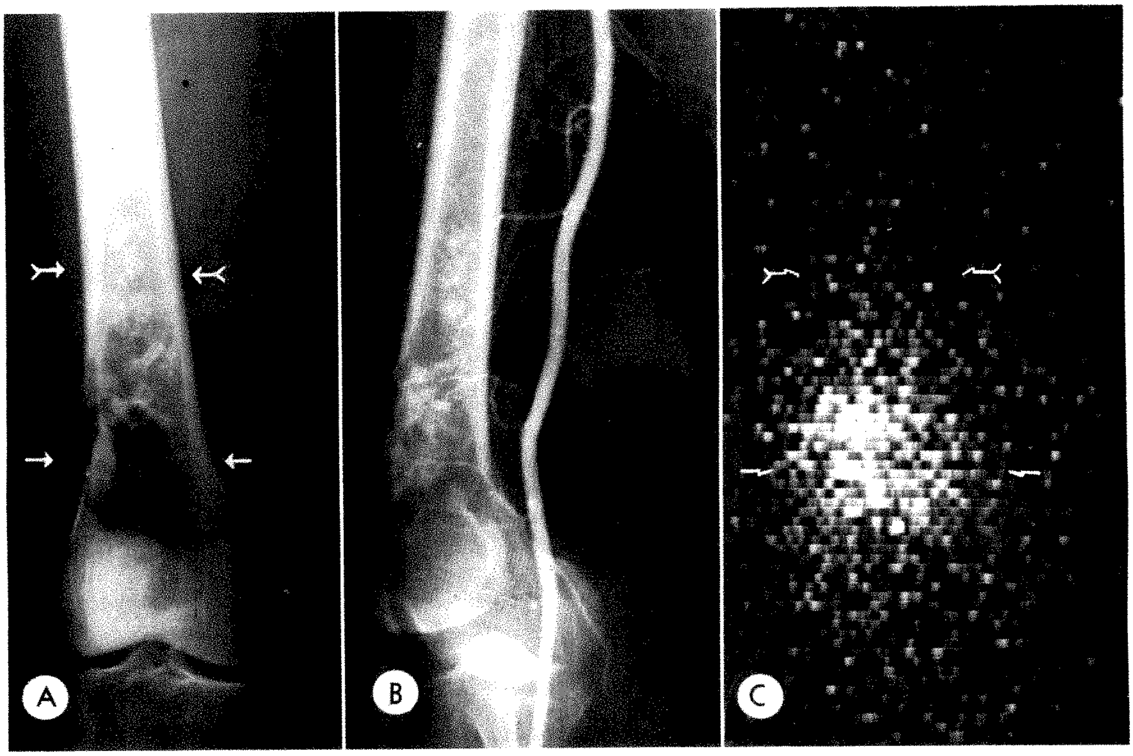
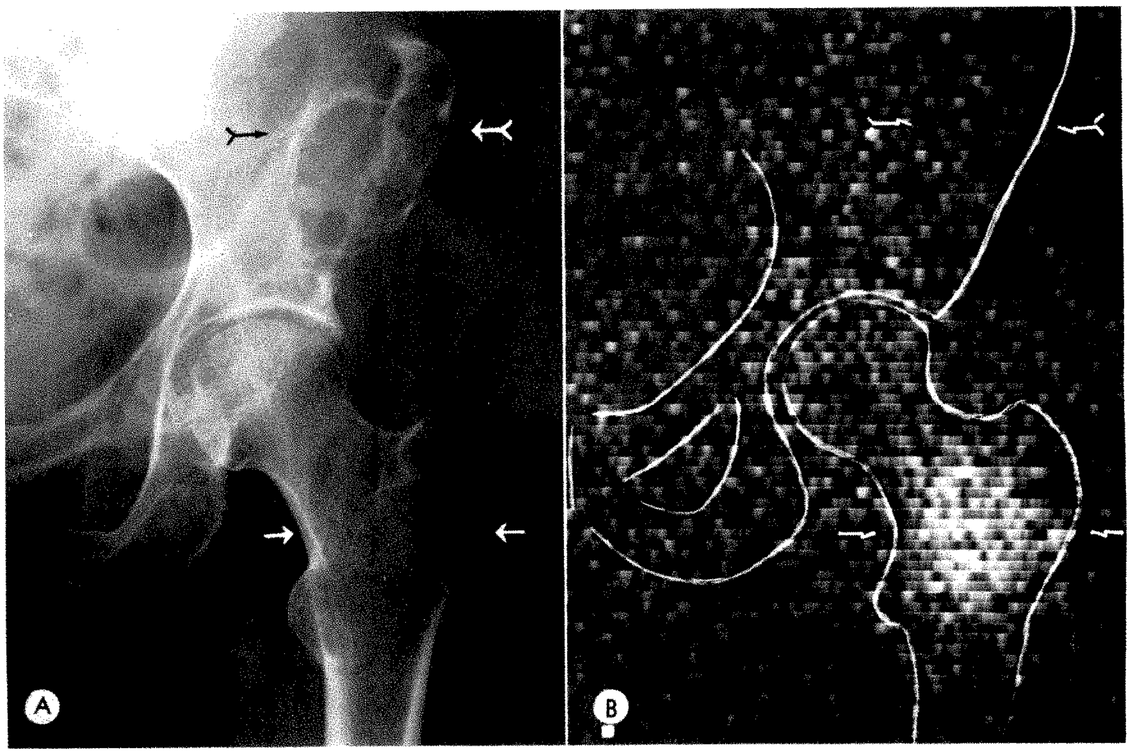


Fig. 7. (*A*) Enchondroma of the right femur in a 61 year old woman. (*B*) Arteriogram reveals normal blood supply to the femur. (*C*) Scintigram shows increased radioactivity in the distal tumor part ↑, where active proliferation is present. There are negative scintigraphic findings in the inactive, proximal tumor part ↑. (Reproduced with permission from: Bessler W., Radioisotope in der Lokalisationsdiagnostik. F. K. Schattauer-Verlag, Stuttgart, 1967, 431.)



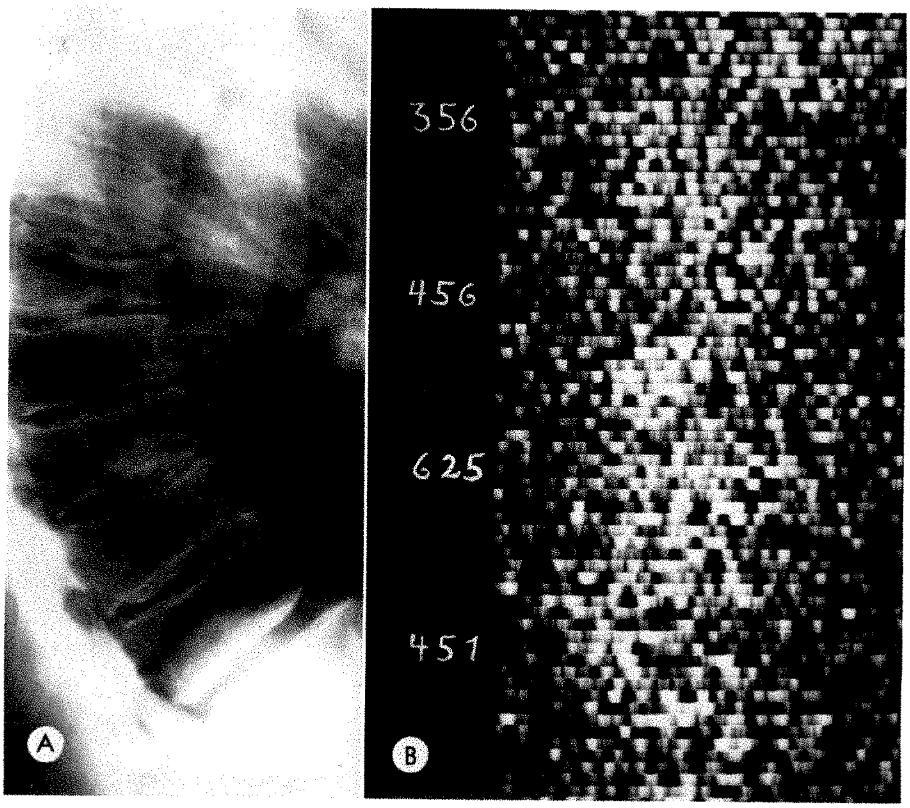


Fig. 9. (*A*) Advanced osteoporosis of the thoracic spine in a 70 year old man. The alkaline phosphatase was elevated to 27 King Armstrong units. (*B*) Increased radioactivity in the lower thoracic spine. The autopsy findings 1 month later confirmed the scintigraphic diagnosis of vertebral metastases of an unknown bronchogenic carcinoma. (The numbers indicate counts per minute.)

elevated (27 King Armstrong units) and since there were no serologic findings suggestive of liver metastases, vertebral metastases were diagnosed and confirmed by autopsy 1 month later. The primary tumor proved to be a bronchogenic carcinoma.

In the table of Figure 10, the findings of 104 skeletal scintigrams of patients with proven or suspected bone metastases were compared with the roentgenographic findings. A + sign indicates monostotic involvement; ++ sign represents cases with polyostotic involvement. Good correlation between both types of examination can be observed for the cases listed in the boxes in thick outline. In the cases in the 3 left lower boxes, scintigraphy supplied better information on the disease than the roentgenographic examination. In 16 cases, skeletal metastases not demonstrated by roentgenography were found by the scintigraphy. Seventeen cases of metastases roentgenologically monostotic were in fact polyostotic according to the scintigraphic findings. The boxes in the right upper corner hold cases with inactive

←

Fig. 8. (*A* and *B*) Scintigraphically inactive metastasis in the left iliac bone of a 44 year old woman with mammary carcinoma treated 2 years previously using cobalt 60 teletherapy ↨. Fresh, active, osteolytic metastasis in the left trochanteric region ↑ is demonstrated. (Reproduced with permission from *Fortschr. a. d. Geb. d. Röntgenstrahlen u. d. Nuklearmedizin*, 1967, *106*, 431.)

	SC++	SC+	SC-
RX++	27	3	—
RX+	17	18	1
RX-	5	11	22

104 SKELETAL SCINTIGRAMS AND ROENTGENOGRAMS

Fig. 10. Comparison between roentgenographic (RX) and scintigraphic (SC) findings in skeletal metastases.

metastases visualized by the roentgenographic examination and undetected by scintigraphy.

CONCLUSIONS

Our experience with skeletal scintigraphy using Sr^{85} leads to the following conclusions:

1. The scintigraphic findings depend on the bone-seeking properties of strontium. An increase in the Sr^{85} accretion rate is usually the result of active osteogenetic function. By scintigraphy it is therefore possible to get direct information about diseases which alter bone metabolism.

2. An increased calcium turnover and its corresponding scintigraphic manifestations of abnormal radiostrontium deposits represent nonspecific reaction of bone which can be caused by neoplastic, inflammatory, degenerative, traumatic, or dystrophic processes.

3. For the differential diagnosis of a bone lesion, roentgenographic studies are of primary importance. However, for the determination of the activity of a pathologic process in the bone, scintigraphy permits complementary functional information, which can be quantitatively measured.

4. In the roentgenographic evaluation of some osteopathies, skeletal scintigraphy and roentgenography are complementary procedures of great value:

(a) to distinguish recent from old healed fractures,
(b) to evaluate possible complications of a healing fracture,
(c) to detect early bone metastases, and
(d) to discover hidden fractures or neoplastic lesions in the skeleton.

SUMMARY

Scintigraphy, after application of Sr^{85}, was performed on 200 patients with different pathologic conditions of the skeleton. Radioactive areas can be noted at bone sites with increased calcium avidity. This function represents a nonspecific reaction occurring in traumatic, inflammatory, degenerative, neoplastic or dystrophic bone lesions. The diagnosis of a skeletal disease depends on the roentgenographic finding. Scintigraphy, however, provides complementary information on the activity of an abnormal bone process.

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THE PLASMA CELL IN RADIOLOGY*

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INCREASED numbers of plasma cells are found in a wide variety of diseases which have roentgenologic significance. The increase may be secondary to an underlying disease or it may be due to autonomous neoplastic proliferation of the plasma cell or a plasma cell precursor as in multiple myeloma, extramedullary plasmacytoma, Waldenström's macroglobulinemia and Fc fragment (Heavy Chain or Franklin's) disease.

There is controversy as to whether the plasma cell arises directly from the reticulum cell or from the lymphocyte or both. With the lymphocyte it is responsible for elaboration of the 4 major groups[12] of immunoglobulins: IgA, IgD, IgG and IgM. Although the immunoglobulins occupy sites in both the beta and gamma region of the electrophoretic scale, they are generally referred to as gammaglobulins and their increase in the serum as hypergammaglobulinemia.[23]

Immunoglobulin molecules are composed of two types of polypeptide chains: a heavy (H) chain and a light (L) chain joined together by disulfide bonds (Fig. 1). Cleavage of the molecule results in two fragments—the Fab or light chain fragment and the Fc or heavy chain fragment. Bence Jones protein is the light chain fragment.[26]

The presence of gammaglobulin (immunoglobulin) can be detected by electrophoretic or immunoelectrophoretic analysis and semiquantitatively by immunodiffusion.

Overproduction of gammaglobulin by antigenic stimulation of the plasma cells results in a generalized or diffuse form of hypergammaglobulinemia as may be found in chronic infection, particularly chronic abscess or granuloma, liver disease, some neoplasms, "collagen" diseases, hypersensitivity and autoimmune diseases, and in rheumatoid arthritis, ulcerative colitis and regional enteritis[2] (Table I). In these diseases the cause of the plasmacytosis and the hypergammaglobulinemia will become apparent with the recognition of the roentgenologic manifestations of the underlying disease.

A second form of hypergammaglobulinemia occurs in which the increase is limited to a single immunoglobulin species, and is related to stimulation or autonomous neoplastic proliferation of a single clone of plasma cells which elaborates only one of the major immunoglobulins or its fragments. This is referred to as monoclonal gammopathy.

In a minority of people with hypergammaglobulinemia of the monoclonal type, this may occur without demonstrable disease and is probably related to a derange-

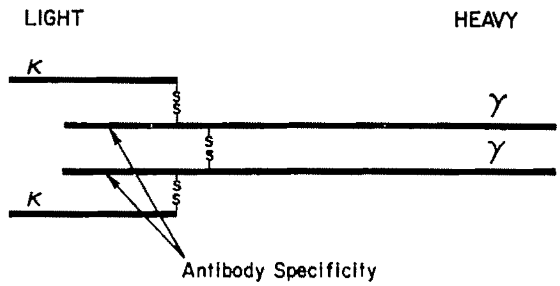

FIG. 1. Schematic diagram of polypeptide chain composition of gammaglobulin (IgG) molecule (modified from Parter[24]). Black horizontal lines represent polypeptide chains linked by disulfide bonds. κ signifies light polypeptide chain and γ signifies heavy polypeptide chain. (Reproduced with permission of *Journal of American Medical Association*.[12])

* Portions of this paper were presented at the Twenty-ninth Midsummer Radiological Conference of the Rocky Mountain Radiological Society, Denver, Colorado, August 17–18, 1967.

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Table I

DIFFUSE HYPERGAMMAGLOBULINEMIA*

1. Infections
2. Liver Disease
3. Some Neoplasms
4. Collagen Diseases
   - Disseminated Lupus Erythematosus
   - Scleroderma
   - Dermatomyositis
   - Polyarteritis Nodosa
   - Sjögren's Syndrome
5. Autoimmune and Hypersensitivity
   - Serum Sickness
   - Hyperimmunization
   - Autoimmune Thyroiditis
   - Erythema Nodosum
6. Rheumatic Fever
7. Rheumatoid Arthritis
8. Ankylosing Spondylitis
9. Regional Enteritis
10. Ulcerative Colitis

* This should not be considered a complete list.

ment in formation of one of the immunoglobulin groups. The majority, however, have either plasma cell myeloma, Waldenström's macroglobulinemia, Fc Fragment disease, leukemia, lymphoma or carcinoma (Table II). About half have plasma cell myeloma.[2,26]

PLASMA CELL MYELOMA (MULTIPLE MYELOMA)

Plasma cell myeloma may occur with or without roentgen evidence of bone disease.[15,25]

1. In general, with proliferation of neoplastic plasma cells within the marrow spaces, there is almost invariably some degree of osteoporosis due to thinning and resorption of the trabeculae (Fig. 2).

2. Very infrequently, there may be osteoblastic stimulation and dense bony sclerosis may occur.[11]

Table II

MONOCLONAL HYPERGAMMAGLOBULINEMIA

1. Plasma Cell Myeloma
2. Waldenström's Macroglobulinemia
3. Fc Fragment (Heavy Chain) Disease
4. Some Leukemias, Lymphomas and Carcinomas
5. Without Evidence of Other Disease

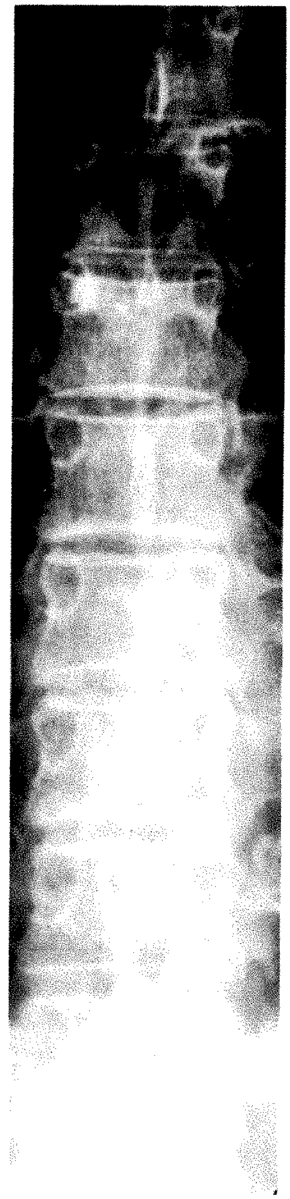

Fig. 2. The classical appearance of multiple, small osteolytic lesions is not the most frequent finding in plasma cell myeloma. Many cases, as in the one illustrated above, show only diffuse osteoporosis, especially of the spine.

3. When frank bone destruction occurs it may simulate the destruction found in other primary or secondary bone tumors and may be (a) geographic, (b) motheaten, or (c) permeative, depending upon

Table III

SKELETAL EVIDENCE OF PLASMA CELL MYELOMA

1. May Show No Evidence of Bone Disease
2. Osteoporosis
3. Osteosclerosis
4. Bone Destruction
a. Geographic
b. Moth-eaten
c. Permeative
d. Cystic

the rate of growth of the tumor (Table III).

4. Where tumor growth is quite indolent, particularly in flat bones, the cortex may expand and this results in a cystic appearance.

Roentgenographically it may be quite impossible to differentiate multiple myeloma from metastatic neoplasm to bone and no single rule is invariable. Multiple myeloma should be suspected, however, when there is multicentric involvement which includes the mandible and scapula; when the verebral bodies are involved but the pedicles are spared[16] (Fig. 3); and when destructive lesions involve the marrow cavity of long bones and of digits.

Soft tissue masses about involved vertebral bodies are said to be more common in myeloma than in carcinoma.[15]

The pelvis is a common site of involvement in myeloma and the lesion may be obscured by gas and fecal material within the bowel and therefore overlooked unless the margins of the sacral foramina are carefully scrutinized. Specific attention should be directed to the "tear drop" of the acetabulum in the anteroposterior view of the pelvis and to the segmentation of the sacrum in the lateral projection if lesions are not to be missed.

Myeloma is next only to metastatic carcinoma and lymphoma as a cause of extradural obstruction.[4]

Because of the derangement of immunoglobulin, bacterial infection, particularly pneumococcal lobar pneumonia, is not an uncommon presenting symptom in patients with plasma cell myeloma (Fig. 4).

The kidney may be affected in multiple myeloma by deposition of proteinaceous material (including Bence Jones protein) within the lumen of the tubules, within epithelial cells lining the tubules, by amyloid involving the kidney parenchyma, and by calculi secondary to hyperuricemia and hypercalciuria.[27]

Amyloidosis, resembling the primary type occurs in 8 to 15 per cent of cases of multiple myeloma.

Recent evidence appears to indicate that the danger of intravenous pyelography is related to dehydration prior to the ex-

Fig. 3. Plasma cell myeloma is second to metastatic carcinoma and lymphoma as a cause of spinal epidural block. The presence of pedicle destruction in this case emphasizes that its absence is not invariable in myeloma. Although pedicle involvement was found in only 14.8 per cent of the cases of Jacobson *et al.*,[16] it occurred in 36.3 per cent in the series of Cohen, Svien and Dahlin.[9]

amination rather than to the urographic contrast agent.[24]

Plasma cell myeloma may appear to be "solitary" and unusual cases with even 34 and 22 year cures have been reported,[32] but the consensus appears to indicate that so-called "solitary" myeloma almost invariably becomes disseminated.[4,9,25]

EXTRAMEDULLARY PLASMACYTOMA

Neoplastic proliferation of plasma cells may occur without bone disease. The tumor, termed extramedullary plasmacytoma, has a particular predilection for the upper respiratory tract, especially the nasopharynx, and the oral cavity. It may arise in unusual sites including the stomach (Fig. 5), thymus, kidney, ovary, lung, mediastinal lymph nodes and intestines.[4,20] This is not surprising since the plasma cell arises from the reticuloendothelial system

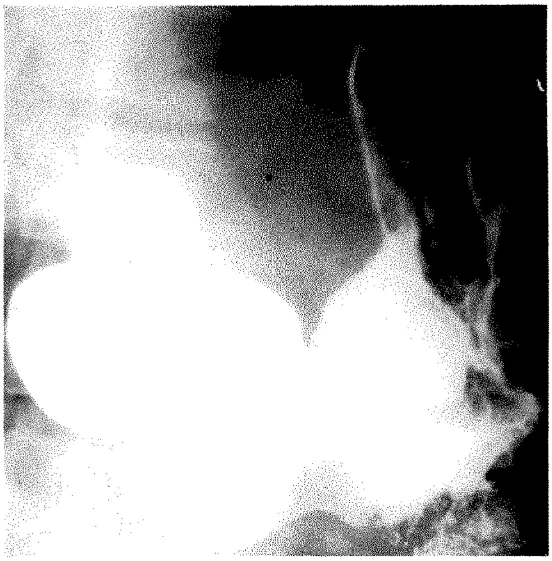

Fig. 5. Extramedullary plasmacytoma is most common in the nasopharynx and oral cavity, but it can occur in the thymus, mediastinal lymph nodes, lung, intestines, kidney, ovary or in the stomach as in this case of a 51 year old male with extramedullary plasmacytoma of the greater curvature of the stomach with peritoneal implants but without systemic or osseous myeloma. (Courtesy of Dr. Alfred Den, Denver Veterans Administration Hospital.)

which is widespread throughout the body. As in "solitary" myeloma, bony dissemination almost invariably occurs.

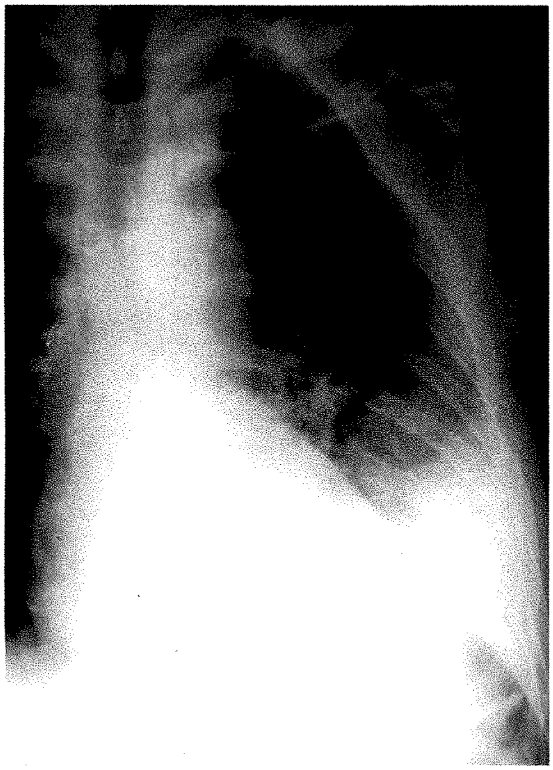

Fig. 4. Pneumococcal lobar pneumonia is a frequent presenting symptom in plasma cell myeloma because of the associated derangement of formation of immunoglobulin.

WALDENSTRÖM'S MACROGLOBULINEMIA

In Waldenström's macroglobulinemia there is marked overproduction of the IgM species of immunoglobulin. This is due to a proliferative disorder of the reticuloendothelial system in which the neoplastic cell is a reticulum cell capable of differentiating into plasmacytic or lymphocytic lines. The neoplastic cells have variously been described as "plasmacytoid lymphocytes" or "lymphocytoid plasmacytes." The disease is characterized by lymphadenopathy and hepatosplenomegaly and has a clinical course resembling malignant lymphoma. As in myeloma, amyloidosis occurs.[13,31]

Lymphangiography may show large lymph nodes with an increased uptake of the contrast material similar to the "typical" lymphoma pattern.[21]

FC FRAGMENT DISEASE

A related disease, Fc Fragment (Heavy Chain or Franklin's) disease has been described. This also pursues a course resembling malignant lymphoma but the neoplastic cell elaborates only the heavy chain fragment rather than the entire immunoglobulin molecule.[26]

OTHER NEOPLASIA

Monoclonal gammopathy, apparently associated with plasmacytosis and occasionally with amyloidosis,[5] may occur infrequently in a variety of neoplasms. Most have arisen in the rectosigmoid, prostate, oropharynx or breast, but 2 cases of hepatic bile duct carcinoma and single cases of carcinoma of the stomach, jejunum, pancreas, uterus, bladder and a case of chronic myelogenous leukemia have been reported.[26] Recently cases of bronchogenic carcinoma have also been reported.[7,8]

AMYLOIDOSIS

Amyloid consists of a polypeptide chain and an intrafibrillar cementing polysaccharide. Although it is tempting to consider the protein moiety as being the immunoglobulin molecule or its light chain fragment, it would appear that this is not always true, particularly in the familial forms of amyloidosis and probably not even in all of the sporadic primary forms, nor in senile cardiac amyloid.[28]

It does appear, however, that forms of amyloidosis may be associated with any disease in which benign or malignant proliferation of plasma cells occurs and in which immunoglobulin is formed in excess. In these instances the protein component would appear to be gammaglobulin or light chain.

A useful current clinical-pathologic classification of amyloidosis is shown in Table IV, as modified slightly from Kenney and Calkins.[19] This appears more useful than the older classifications.[10]

Secondary amyloidosis occurs in the presence of a chronic underlying disease. In the past, chronic suppurative and inflammatory diseases such as osteomyelitis, tuberculosis and bronchiectasis were considered to be the usual etiologic factors. Today, rheumatoid arthritis seems to be the most common cause of secondary amyloidosis. Currently other common accompanying diseases are disseminated lupus erythematosus, scleroderma, polyarteritis nodosa, ulcerative colitis, regional enteritis and certain neoplasms, including Hodgkin's disease and hypernephroma.

In secondary amyloidosis, the amyloid seems to be the result of prolonged antigenic stimulation of the plasma cells with formation of excess immunoglobulin which is combined with a polysaccharide *in situ* within the "typical" organs—usually the liver, spleen and kidney.

Roentgenographic diagnosis of secondary amyloidosis is therefore limited to enlargement of these organs in a patient who also shows evidence of an appropriate accompanying disease. When the kidneys are involved they may additionally show some spreading of the infundibula and calyces[6] but usually there is no gross calyceal distortion.

In the primary sporadic form associated with plasmacytosis and in that form found with multiple myeloma or Waldenström's macroglobulinemia, the distribution is usually, but not necessarily, distinctive, *i.e.*,

Table IV

AMYLOIDOSIS

- A. Primary Amyloidosis
  - 1. Genetic
    - a. With Familial Mediterranean Fever
    - b. Primary Familial Amyloidosis of Andrade and Rukavina
  - 2. Sporadic
    - a. Typical (Pattern Similar to Secondary Amyloidosis)
    - b. Atypical (Diffuse Pattern)
  - 3. Tumor Forming
- B. Secondary Amyloidosis
- C. Amyloidosis Associated with Multiple Myeloma and Waldenström's Macroglobulinemia
- D. Senile Cardiac Amyloidosis

"atypical." There may be involvement of the heart, lungs, gastrointestinal tract, paranasal sinuses, spinal epidural space, skeletal muscle, joints, bone, skin and nerves.[3,14,17,22,29] Unilateral or bilateral carpal tunnel syndrome is frequent. "Typical" organs may also be involved.

Roentgenographically the heart may be enlarged and the lungs congested. Fluoroscopically the appearance may simulate pericardial effusion due to diminished pulsations.

The lungs may show a stippled, interstitial infiltration varying in degree related to amyloid deposited within the walls of the pulmonary vessels.[29] Amyloid must be considered in the differential diagnosis of disseminated interstitial pulmonary disease.

The gastrointestinal tract may be involved from the tongue to the rectum. Unlike scleroderma, amyloid infiltrates striated muscle and may impair the pharyngeal phase of deglutition in addition to the involvement of the esophagus which occurs in both scleroderma and amyloid.

The appearance of the stomach may simulate linitis plastica or actual nodules may be found.

In the small intestine there is generalized dilatation with symmetric thickening of the valvulae conniventes. The transit of barium through the small intestine may be delayed for days. Most distinctive is the very marked thickening of the bowel wall simulating separation of the loops (Fig. 6).

Destructive osseous changes secondary to invasive amyloid deposits within the hip joints have been demonstrated[1,17] and in one case of osseous plasmacytoma of the pelvis, the amyloid deposit was so extensive as to obscure the underlying myelomatous nature of the tumor.[22]

Calcifications, similar to those found in dermatomyositis and scleroderma have been observed in extensive subcutaneous deposits of amyloid accompanying Waldenström's macroglobulinemia.[5]

Tumoral and nodular amyloidosis, like cardiac amyloidosis, may accompany the primary sporadic form or may be present as an isolated finding. In the latter setting the upper respiratory tract is most frequently involved but it may also affect the eye, tongue, larynx, lower respiratory tract, urinary bladder, pancreas, gasserian ganglion and thyroid.

Fig. 6. The small intestine may be involved in either primary amyloidosis or in amyloidosis associated with plasma cell myeloma or macroglobulinemia. This patient with myeloma showed dilatation of the small bowel, thickening of the valvulae conniventes, delayed transit and marked separation of the loops due to thickening of the bowel wall.

In the tracheobronchial tree the amyloid is deposited beneath the mucosa, forming ridges, plaques and nodules which, if not characteristic, may at least be suggestive of the disease because of its diffuseness throughout the lower respiratory tract.[18]

Roentgenographically, solitary or multiple amyloid tumors of the lung frequently show calcification and even metaplastic ossification. This is most frequently ob-

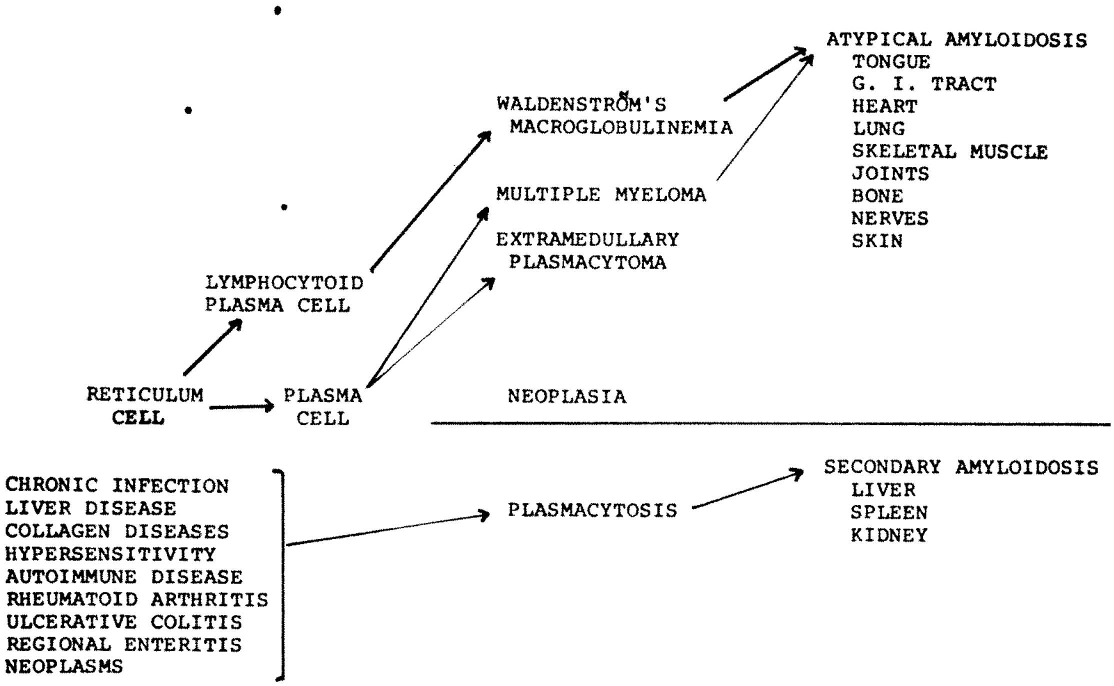

Fig. 7. The plasma cell and its products in relationship to the immunoglobulins and their components.

served in the lung, but calcification has also been described pathologically in amyloid tumors of the tongue, larynx, stomach, endocardium and adrenals.[30]

SUMMARY

The plasma cell and its products, the immunoglobulins and their components, play a role in disease capable of roentgenologic recognition (Fig. 7).

The plasma cell arises from the reticulum cell or from the lymphocyte. It elaborates the 4 major species of immunoglobulin.

Neoplastic proliferation of the plasma cell results in plasma cell myeloma or extramedullary plasmacytoma. Neoplastic proliferation of "lymphocytoid plasmacytes" results in Waldenström's macroglobulinemia, if an immunoglobulin is formed, or in Fc fragment disease if only the heavy chain fragment is elaborated.

These neoplasias may be associated with amyloidosis which appears to be a combination of an immunoglobulin fragment with a polysaccharide.

Plasmacytosis and hypergammaglobulinemia may also result from chronic antigenic stimulation in a number of diseases, es pecially rheumatoid arthritis, chronic ab scesses and granulomata, the collage vascular disorders, certain neoplasms, an in ulcerative colitis and regional enteritis among others. Amyloid may also compli cate these diseases but is of the so-calle secondary type.

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PERMANENT RADIATION MYELOPATHY*

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PERMANENT radiation myelopathy is recognized as a possible complication of radiation therapy whenever the spinal cord is included in the field of irradiation. There are a moderate number of reported cases in the literature.[1,2,4,5,9,10,11,12,13,16-23]

This study represents our experience in 6 cases of radiation myelopathy as a complication in treatment of inoperable carcinoma of the lung. The damage, therefore, in all cases occurred in the thoracic spinal cord. We have no histologic proof in any of the patients but by history, physical, laboratory and roentgenographic examination, we believe that we are able to present these as classic cases of radiation myelopathy.

CLINICAL MATERIAL

From 1959 to the latter part of 1963, 207 patients with inoperable carcinoma of the lung were treated at the Mallinckrodt Institute of Radiology. Treatment was done on an Allis-Chalmers betatron operated at 22.5 mev., and all patients were treated to a midplane dose of at least 2,500 rads. Not included in the 207 patients are those only observed or treated to less than 2,500 rads. Our basic treatment plan at that time was to deliver a midplane dose of 4,000 rads in 3 weeks in 15 treatments through parallel opposing anterior and posterior ports. This plan was successfully accomplished in 86 per cent of the 207 patients. From the 178 patients treated to approximately 4,000 rads in 3 weeks, we have observed 6 cases of radiation myelopathy developing in the 48 patients who lived over 1 year. All patients originally had biopsy-proven malignant tumor. Biopsy specimens were interpreted as carcinomas in 3 patients and anaplastic carcinoma in 2 patients. The other case was originally diagnosed histologically as undifferentiated carcinoma of bronchial origin, but was later rediagnosed as malignant lymphoma because of consideration of the response to radiation therapy and the patient's subsequent course. In all patients the segment of thoracic spinal cord irradiated was greater than 10 cm. and the entire width of the cord was irradiated in 4 of the 6 patients who developed myelopathy. The latent period from completion of therapy to the earliest symptom ranged from 12 to 35 months. Two patients died from complications arising as a direct result from myelopathy 29 and 48 months following the completion of therapy. The other 4 patients are alive from 30 months to 68 months without demonstrable evidence of malignant disease. Myelographies were done in 5 of the 6 patients and all interpreted as normal.

CLINICAL FEATURES

From the cases reported in the literature and in our experience, the usual latent period is between 1 and 2 years following the completion of therapy. The onset of symptoms is usually insidious but the rate of progression of symptoms is variable. There appears to be no correlation between rate of progression and severity of illness. The entity described as transient radiation myelopathy by Jones[14] and Boden[5] clinically appears different from the progressive form of myelopathy. In the present series, none of the patients with permanent radiation myelopathy had previous symptomatology suggestive of transient radiation myelopathy. There are 2 cases of permanent radiation myelopathy reported in the literature which did appear to have symp-

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tomatology suggestive of the early form or transient radiation myelopathy; however, this would appear to be the rare exception rather than the rule. The transient form appears to have a latent period of a few months following the completion of therapy and persists for an average of a few months. In none of the reported cases, however, have the symptoms of progressive radiation myelopathy decreased in severity or disappeared.

CLINICAL COURSE

Radiation myelopathy cannot be differentiated from other forms of myelitis. However, a common course for the disease is to manifest itself as a Brown-Sequard's syndrome. This syndrome or variants thereof was present in 5 of our patients, 2 of whom subsequently developed signs and symptoms of a transverse myelitis. In 3 other patients with a Brown-Sequard syndrome, the degree of myelopathy appears stabilized. This is consistent with what has been seen in other series. The apparent unilateral spinal cord lesion, despite the fact that the whole cord might have been irradiated, causes one to speculate on the pathology of radiation myelopathy and whether the neural injury is due primarily to an effect on nerve cells directly or secondary effects due to damage of connective tissue and blood vessels. It is not within the scope of this study to discuss this problem. We would tend to believe, however, as do the majority of other authors, that the disease appears to be mainly secondary to an effect upon the blood vessels and connective tissue.

Pallis *et al.*[18] point out that three criteria should be met before making the diagnosis of radiation myelopathy.

(a) The spinal cord should have been included in the area irradiated.

(b) The main neurologic lesion should be within the segment of cord exposed to irradiation.

(c) Myelography or necropsy should have excluded cord compression from metastases as the cause of the neurologic disorder.

All of our cases satisfy these criteria except Case VI, on whom we have no myelogram. However, we believe that we are justified in making the diagnosis of radiation myelopathy in this patient on the basis of clinical grounds and subsequent follow-up.

REPORT OF CASES

Case I (Fig. 1). A 46 year old Negro female was admitted to Barnes Hospital in December, 1958, where a diagnosis of inoperable epidermoid carcinoma of the right lung was made. In a period of 21 days and in 15 treatments, through 13×13 cm. anteroposterior and posteroanterior opposing ports, she was treated to a midplane dose of 3,910 rads. The spinal cord received a calculated dose of 3,870 rads in this time. Towards the end of therapy, she developed severe dysphagia. Esophagoscopy was done because of her extreme difficulty in swallowing and marked mucositis was noted. In May, 1960, she developed pneumonia of the right lower lobe which was treated with appropriate antibiotic therapy. Beginning in June, 1960, she became aware of an intermittent burning and tingling sensation in both lower extremities, the left more than the right. This progressed to weakness of both lower extremities, with a foot drop noted on the right. She was admitted to the hospital on November 4, 1960, when a neurologic examination disclosed a sensory level to pin-prick on the left with hypalgesia to the T9 level. There was also motor weakness of the right lower extremity, and more particularly, weakness of dorsiflexion of the right foot. There was also a right extensor toe sign. Vibration and position senses were intact bilaterally. The chest roentgenogram at this time showed shrinkage of the right lung with postirradiation fibrosis. Myelography was performed and interpreted as normal. She was discharged from the hospital essentially unchanged. The neurologic difficulties progressed, however, to a more severe right leg weakness and in April, had progressed to near-complete paraplegia. She was bed-ridden during the last 2 months of her life, and expired at home of pneumonia. There was no evidence of either primary recurrence or metastatic disease at the time of death.

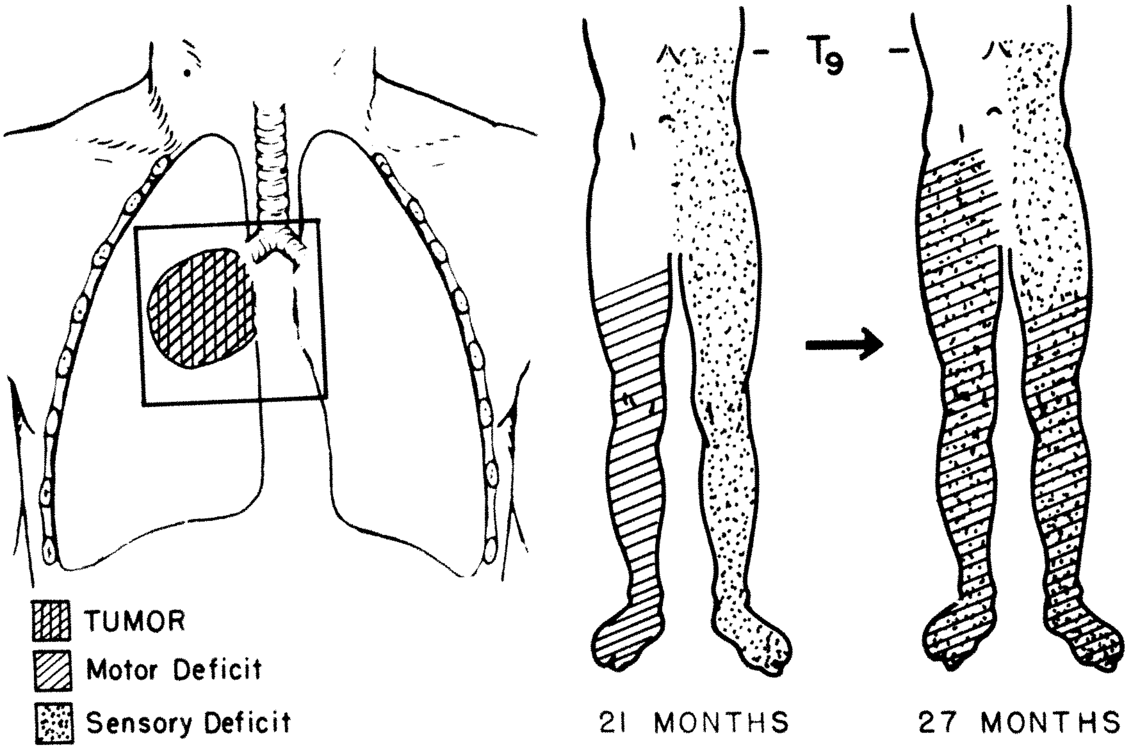

FIG. 1. Case I. A 46 year old Negro female. The tumor dose was 3,910 rads and the spinal cord dose 3,870 rads in 21 days, 15 treatments. The symptoms began 21 months after treatment and progressed from Brown-Sequard syndrome to paraplegia over 8 months. She died 29 months after treatment from complications of paraplegia; there was no evidence of tumor.

CASE II (Fig. 2). A 50 year old white married male was admitted to Barnes Hospital on March 31, 1960, with intermittent chills and fever of one year's duration and a 10 pound weight loss. A chest roentgenogram showed a right superior mediastinal mass with left pleural effusion. Biopsy revealed metastatic carcinoma of bronchial origin. Therapy was administered through opposing ports 15×15 cm. in a period of 18 days and in 15 treatments. He was treated to a midplane dose of 4,000 rads. The spinal cord received a dose of 3,890 rads in this time period. There was marked regression of the tumor on chest roentgenography, and for this reason, it was thought that the lesion might well have been a lymphoma.

He was admitted to Barnes Hospital again on December 6, 1961, with a chief complaint that he had been numb in the lower part of his chest since July of that year. On physical examination, a weakness of both hip extensors and flexors was found, especially on the left, with decreased sensitivity to pin-prick from T4 to L3 on the right and hyperesthesia from T4 to L2 on the left. The left ankle jerk was 3+, the right knee and ankle jerk were 2+. A positive Babinski sign was demonstrated on the left. A myelogram showed no evidence of block or extrinsic impression. Biopsy of a left inguinal lymph node at that time showed hyperplasia.

He was admitted again to the hospital on November 4, 1964, for headaches, shaking chills and fever. A complete work-up at that time failed to show evidence of lymphoma.

Physical examination at the present time shows a slight left foot drop with increased dependent reflexes on the left. A positive Babinski sign is present on the left. There is only minimal ability to dorsiflex the left foot and toes, and slight atrophy in the left tibialis anterior muscle. There is decreased vibratory sensation in both ankles and decreased sensation to touch, pin-prick and soft touch over T4 to L4 on the right. Rectal examination reveals good sphincter tone. Chest roentgenogram shows no change in the past 5 years.

CASE III (Fig. 3). A 61 year old white male

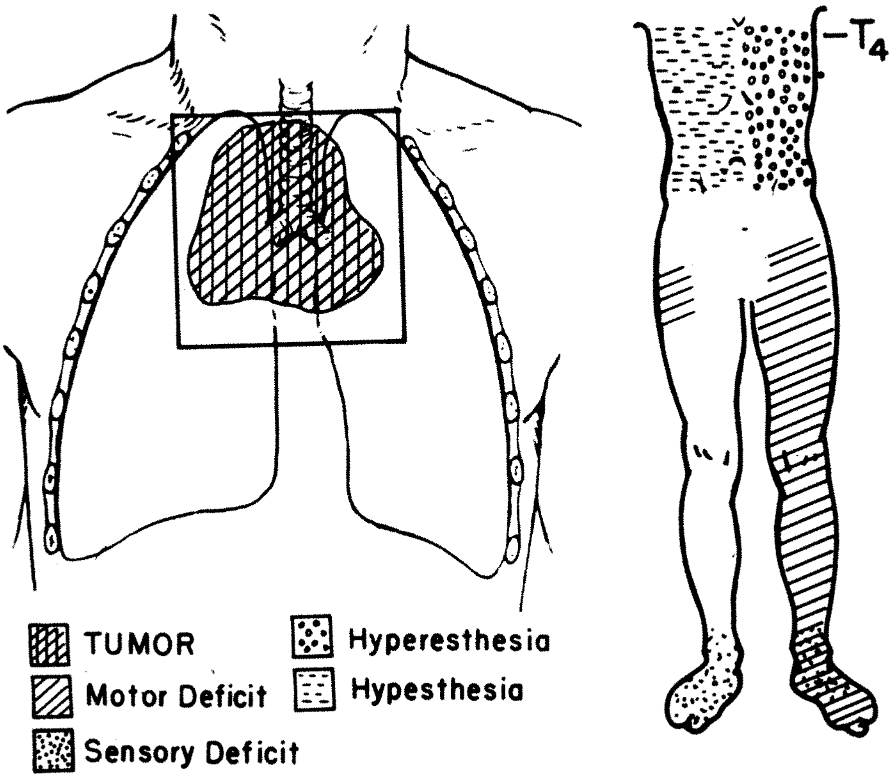

FIG. 2. Case II. A 50 year old white male. The tumor dose was 4,000 rads and the spinal cord dose 3,890 rads in 18 days, 15 treatments. The symptoms began 16 months after treatment. Has Brown-Sequard syndrome which is unchanged to present time. He is alive 68 months after treatment without evidence of malignancy.

entered Barnes Hospital on August 21, 1961, with a chief complaint of a mass in the right neck and in the right lung. Chest roentgenogram showed a large mass in the right upper lobe impinging on the mediastinum, with evidence of hilar lymphadenopathy depressing the right main stem bronchus. A supraclavicular lymph node biopsy demonstrated anaplastic carcinoma. Eighteen mg. of nitrogen mustard was given on August 23 and 24, 1961. The patient was then referred for roentgen therapy. He was treated by opposing anterior and posterior fields measuring 11×12 cm., and in 27 days and in 19 treatments, received a midplane dose of 4,550 rads. He was also treated to his right supraclavicular area through an 8×8 cm. port utilizing cobalt 60 irradiation to a calculated tumor dose of 4,000 rads. Care was taken on this port to exclude the spinal cord from the field of irradiation. Progressive dysphagia was noted during the course of treatment, to near-complete inability to swallow all foods. This dysphagia continued up until 6 months following the completion of therapy. A barium swallow examination done in April, 1962, showed moderate stenosis of the upper one-half of the thoracic esophagus. At that time, the esophagus was dilated under direct esophagoscopic visualization. He did quite well and was near-asymptomatic up to August, 1964, when he noticed the slow onset of numbness in his right heel. This progressed rapidly and on successive visits the symptoms progressed to his right leg to the scrotum, involving serially the medial aspect of his left leg. In 1 month he became paraplegic and incontinent. On physical examination in November, 1964, he was noticed to have bilateral Babinski signs, with decreased vibratory sensation bilaterally and a mild hypalgesia in both extremities. Bowel function was poor, with poor rectal tone. Myelography was performed and interpreted as normal. An enlarged prostate was noted by rectal examination. A subsequent transurethral resection was done for benign prostatic hypertrophy; however, this did not appear to aid his

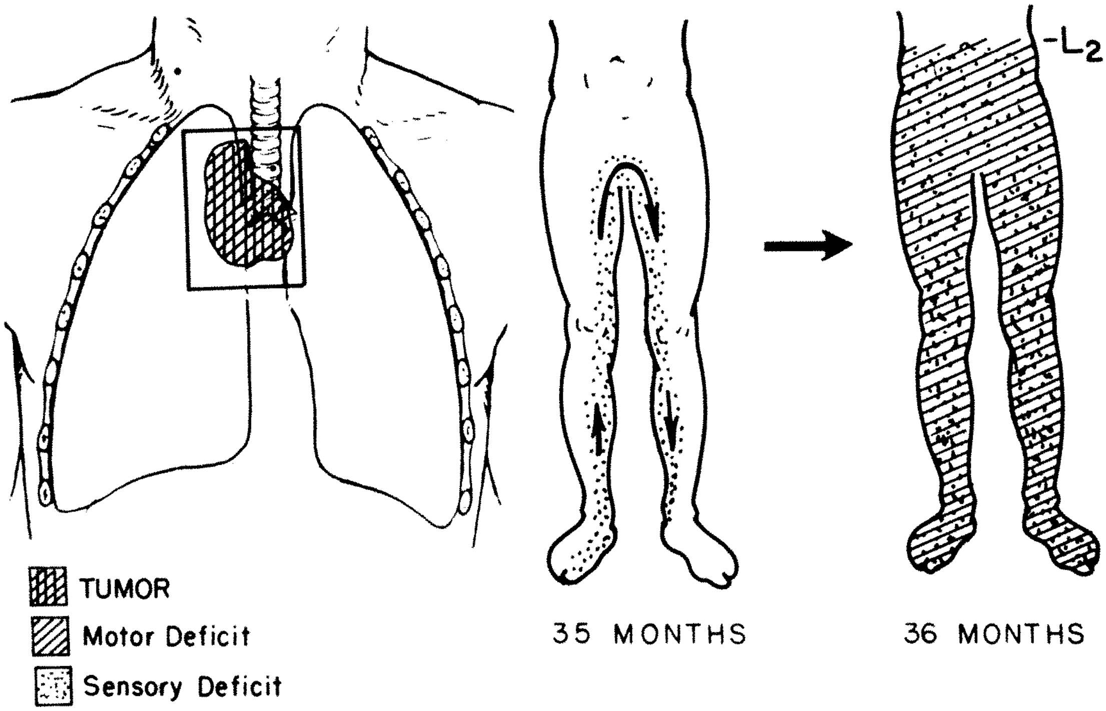

FIG. 3. Case III. A 61 year old white male. The tumor dose was 4,550 rads and the spinal cord dose 4,850 rads in 27 days, 19 treatments. The symptoms began 35 months after treatment and progressed rapidly from bilateral sensory changes to paraplegia. He died 48 months after treatment without evidence of malignancy.

ability to void. The patient expired at home of pneumonia and cachexia, without evidence of tumor 48 months following his radiation treatment.

CASE IV (Fig. 4). A 52 year old Negro male was admitted to Barnes Hospital in May, 1962, when he was found to have a left upper lobe infiltrate. Washings obtained at bronchoscopy showed atypical cells, diagnostic of epidermoid carcinoma. There was also erosion of the fourth rib anteriorly noted on chest roentgenography. In 21 days and in 16 treatments, he was irradiated to a midplane dose of 3,950 rads on the betatron through opposing anteroposterior and posteroanterior left upper chest ports measuring 15×15 cm. The shoulder and larynx were protected by lead blocks. In August, 1963, he began complaining of ill-defined tingling sensations in the left shoulder and hip. This remained somewhat static, with no evidence of neurologic deficit until April, 1964, when he was noted to have weakness of the left leg and questionable sensory loss in the right leg. A diagnosis of Brown-Sequard's syndrome was made at that time. A myelogram was normal. Since April, 1964, his neurologic status has remained essentially unchanged, except for disappearance of pain.

Generalized weakness is more of a problem at this time. On physical examination, there is an obvious loss of volume of the left hemithorax with atrophy of the pectoral muscle on the left. There is fair rectal sphincter tone, with voluntary control. Definite weakness of the left lower extremity is present, and there is moderate weakness of the left upper extremity, absent vibratory sensations in both legs, and absent positional sense in the left lower extremity. A questionable decreased sensation to pin-prick in the right lower extremity is also noted. There is hyperreflexia on the left, with no evident Babinski sign. A chest roentgenogram shows no evidence of change over the past 4 years.

CASE V (Fig. 5). A 40 year old white male was admitted to Barnes Hospital in May, 1962, because of a 6 week history of cough, chest pain and hemoptysis. Chest roentgenograms showed a large mass in the right upper lobe, with metastases to the azygous node and extension into the hilus and mediastinum. The patient was ex-

FIG. 5. Case v. A 40 year old white male. The tumor dose was 4,050 rads and the spinal cord dose 4,070 rads in 21 days, 16 treatments. The symptoms began 12 months after treatment. Has Brown-Sequard syndrome which is unchanged to present time. He is alive 54 months after treatment without evidence of malignancy.

area received a calculated tumor dose of 4,370 rads. Moderate dysphagia was present which lasted up to one month following the completion of therapy. In May, 1964, she had herpes zoster in the left 9th and 10th dermatomes which lasted approximately 1 month. In November, 1964, she began to have early signs of a Brown-Sequard's syndrome, with slight numbness in the right lower extremity, and with minimally hyperactive dependent reflexes in the left lower extremity. There was also an early suggestion of decreasing muscle mass in the left lower extremity. The patient also gave a history of discrepancy in sensation to heat and cold in the lower extremities.

On January 5, 1965, she was again seen and there appeared to be a definite progression over the past 2 months. There was numbness and loss of temperature sensation in the right lower extremity. Left dependent reflexes were increased and there was decreased muscle mass in the left calf. There was still some pain in the left 9th and 10th dermatomes. Chest and dorsal spine roentgenograms showed no definite change in the appearance of the chest, although recurrence of the tumor could not definitely be ruled out. Myelography was not performed. A lumbar puncture was normal. The findings were thought to be best explained by radiation myelopathy. In May, 1965, she returned with evidence of bilateral lower extremity weakness and early spasticity. It was felt that the myelopathy was progressing. A chest roentgenogram showed no change in the past 2 years. Lumbar and thoracic spine roentgenograms revealed no evidence of metastatic disease. The patient has developed a spastic paraplegia with a level at T9.

The features of the clinical cases are summarized in Table I.

INCIDENCE

Atkins and Tretter[1] give an excellent review of previous studies in which, in addition to time-dose consideration, they discuss the subject of incidence of myelopathy. The exact incidence of myelopathy occurring when the spinal cord is irradiated to a given dose is rather difficult to determine. Two factors responsible for this are the poor survival rates of patients with disease for which the spinal cord might be included in the field of irradiation, and the delay of onset of myelopathy, which in 1 reported case has been as long as 70 months. In our series, we observed 6 cases of dorsal myelopathy in a total of 48 patients surviving 1 year, for an incidence of 12.5 per cent. This would appear to agree with the incidence as reported in other series.

TIME-DOSE RELATIONSHIPS

As in any other tissue, the degree of radiation change in the spinal cord is time-dose-volume dependent, excluding the factor of individual tissue sensitivity. Boden,[6] in 1950, drew up a time-dose plot for tolerance of the cord according to the method of Strandqvist. Pallis, Louis and Morgan,[18] in 1961, estimated the tolerance level to be in the range of 20 per cent below that suggested by Boden. Our dose to the cord of approximately 4,000 rads in 3 weeks lies well above that suggested by Pallis and his co-workers, and even that recommended by Boden. As previously mentioned, this study includes those cases treated up until the latter part of 1963.

FIG. 6. Case VI. A 41 year old white female. The tumor dose was 4,300 rads and the spinal cord dose 4,370 rads in 23 days, 13 treatments. The symptoms began 12 months after treatment and have progressed from Brown-Sequard syndrome to paraplegia at present time. She is alive 30 months after treatment without evidence of malignancy.

Table I

SUMMARY OF CASES

Case No.	Age	Tumor Dose (rads)	Spinal Cord Dose (rads)	Time (days)	No. of Treatments	Length of Spinal Cord Treated (cm.)	Location of Spinal Cord Treated	Onset of Radiation Myelopathy (months)	Status of Patient
I	46	3,910	3,870	21	15	13	D6–D11	21	Brown-Sequard; paraplegia. Dead (paraplegia), 29 months; no evidence of tumor
II	50	4,000	3,890	18	15	15	D1–D7	16	Brown-Sequard. Alive, tumor free; 68 months
III	61	4,550	4,850	27	19	12	D3–D9	35	Sensory loss; paraplegia. Died (paraplegia), 48 months; no evidence of tumor
IV	52	3,950	3,950	21	16	15	D2–D8	14	Brown-Sequard. Alive, tumor free; 51 months
V	40	4,050	4,070	21	16	14	D1–D8	12	Brown-Sequard. Alive, tumor free; 54 months
VI	41	4,300	4,370	23	13	15	D3–D10	12	Brown-Sequard; paraplegia. Alive, tumor free; 30 months

At that time, we began irradiating patients with lung cancer through anterior ports only, except in cases where the tumor was in the posterior one-third of the lung field. Thus, following the change in treatment plan in 1963, in delivering the midplane dose of 4,000 rads in 3 weeks, the spinal cord receives a dose of 3,100 rads in the same period of time (Fig. 7 and 8). This dosage to the spinal cord of 3,000 rads in 21 days lies between the curves drawn by Boden and Pallis *et al.* Since converting to this new treatment plan, we have observed no new cases of radiation myelopathy; however, there has been an insufficient time elapsed to make definite conclusions concerning the results of our present dose to the spinal cord. In the case of posterior chest field tumors, the patient is treated using anteroposterior and posteroanterior opposing ports, but the dose is regulated so that the spinal cord does not receive more than 1,000 rads per week in 3 or 5 fractions per week.

It is interesting to note that of the 6 patients developing myelopathy late, 3 had severe esophagitis during therapy. Two patients subsequently required esophagoscopy and dilatation. It is of further interest, however, to note that 2 of the patients who developed paraplegia were from the 3 who developed severe esophagitis. The third patient with transverse myelitis and paraplegia had herpes zoster of the affected spinal segments just 2 months prior to onset of myelopathy. While it is common for patients to develop some mild esophagitis during radiation therapy for carcinoma of the lung, it is unusual to develop such severe esophagitis that esophageal dilatation is necessary. We have carefully reviewed the dosage calculations on these patients and feel certain that the occurrence of severe esophagitis cannot be explained on the basis of incorrect dosage of radiation. These findings, therefore, are worthy of note since they would seem to implicate, in part at least, individual radiosensitivity as the cause of the esophagitis and severe myelopathy.

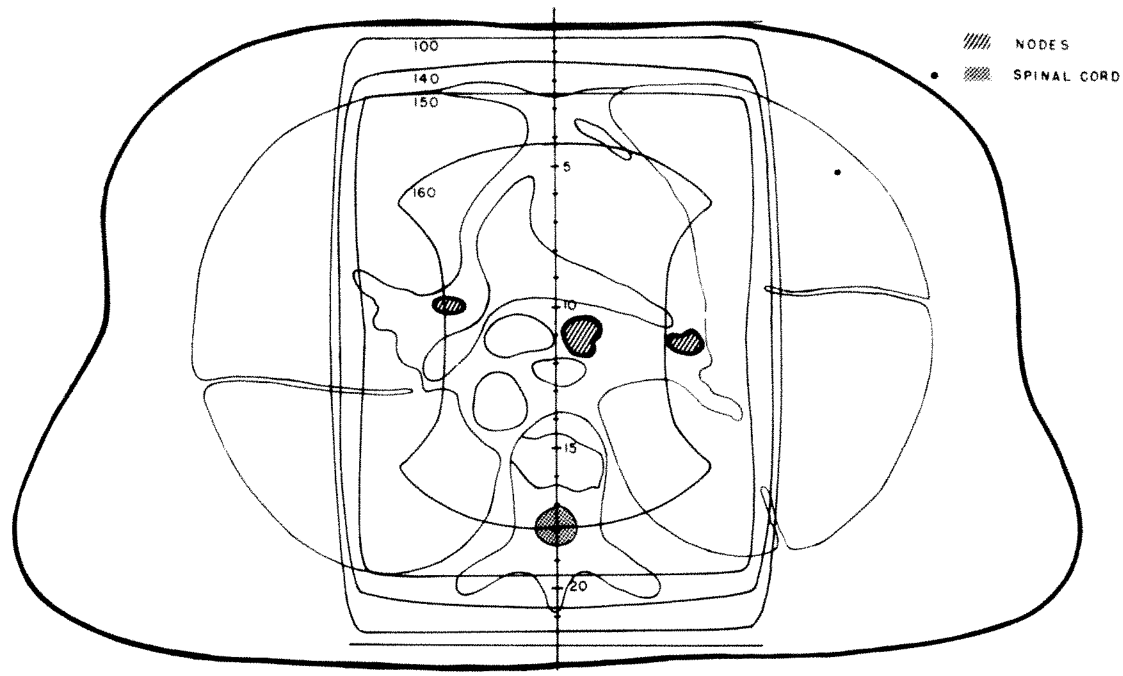

Fig. 7. Dose distribution of anterior and posterior betatron fields. Cross section at the level of the 5th dorsal vertebra. Patient contour 22 cm. in anteroposterior diameter. Note that the spinal cord received a dose equivalent to the tumor.

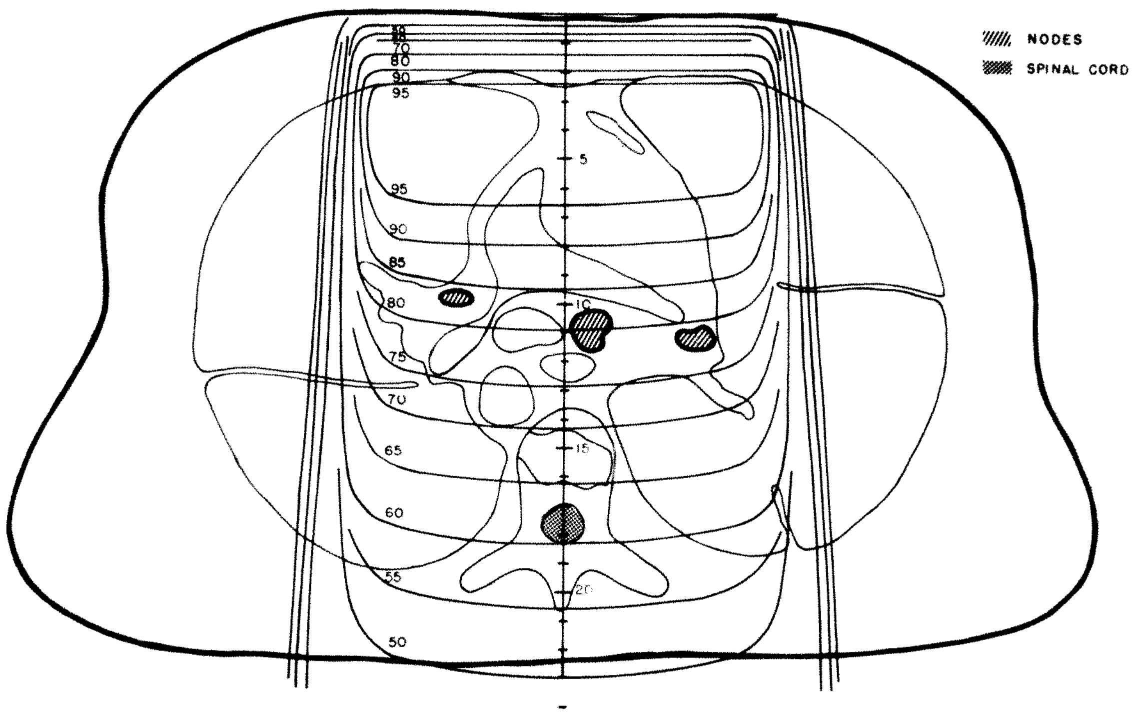

Fig. 8. Dose distribution of anterior field. Note that the tumor received 75 per cent of maximum dose and the spinal cord 60 per cent of maximum dose. The spinal cord therefore received 80 per cent of the tumor dose.

SUMMARY

Six cases of radiation myelopathy occurring as a complication of radiation therapy of inoperable carcinoma of the lung are reported. The segment of the thoracic spinal cord irradiated was greater than 10 cm. in all patients. The dose to the spinal cord was in the range of 4,000 rads in 3 weeks, given in approximately equal fractions 5 times a week. All treatments were done on an Allis-Chalmers betatron operating at 22.5 mev. The treatments were equally given through anteroposterior and posteroanterior opposing ports. The incidence of radiation myelopathy in our series of 48 one year survivors was 12.5 per cent. Because of this complication, we have modified our treatment plan.

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THERMOGRAPHY AND THE VENOUS DIAMETER RATIO IN THE DETECTION OF THE NON-PALPABLE BREAST CARCINOMA*

By IRWIN M. FREUNDLICH, M.D.,† JOHN D. WALLACE, A.B.,‡ *and* GERALD D. DODD, M.D.§

DESPITE surgical and medical advances in the treatment of breast carcinoma, the mortality rate remains unchanged.[1,12,13] It has been established that patients without axillary lymph node metastases at the time of surgery have a greater chance of survival than those with axillary lymph node involvement and the percentage of patients with axillary lymph node metastases increases directly with the size of the lesion.[8,15] In addition, it has been reported that lesions discovered by mammography, in particular those too small to be detected by palpation, have a lower incidence of axillary lymph node metastases.[3,4,7,17] In these patients, therefore, an improved mortality rate may be presumed. In order to detect the small, preclinical lesions, some type of population screening is mandatory. Shapiro and his co-workers[14] reported an improved mortality rate in a large series of patients screened by mammography. Mammography, however, because of the time needed to carry out and interpret the roentgenograms, probably would be limited to high risk groups. Thermography, on the other hand, is rapidly performed and interpreted. A thermogram is quickly scanned for suspicious areas and may be quite suitable for population screening.

THERMOGRAPHY

The thermogram is a pictorial representation of infrared emission from the skin. Lawson[9] in 1956 was the first to apply these principles to the detection of breast cancer. Later work by Lloyd-Williams *et al.*[11] and by Gershon-Cohen and his group[5,6] further demonstrated the thermogram's clinical potential. In addition to its potential usefulness as a screening method, the thermogram is particularly helpful in excluding malignancy in the premenopausal patient or in any patient whose breasts are dense and difficult to interpret by mammography and clinical palpation. Wallace and Dodd,[16] using a Smith Pyroscan Unit, modified the thermographic procedure. Because the eye perceives more shades of gray at the dark end of the black to white scale, the polarity of the thermogram was reversed so that warm areas are

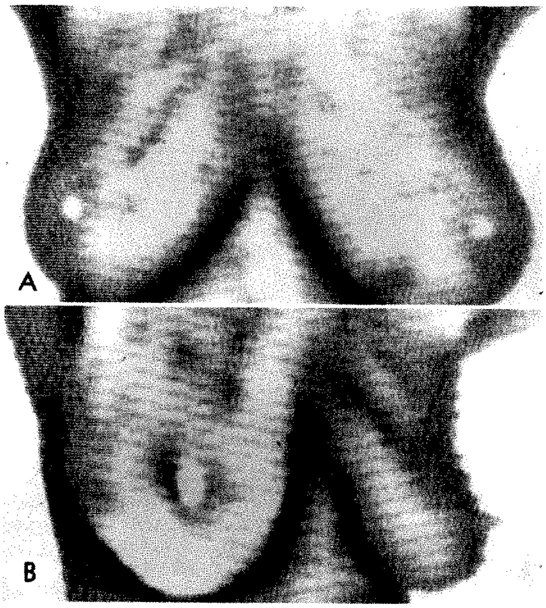

Fig. 1. (*A*) Normal thermogram, anterior view. (*B*) Normal thermogram, oblique view of right breast.

* Presented at the Sixty-eighth Annual Meeting of the American Roentgen Ray Society, Washington, D. C., September, 26–29, 1967.
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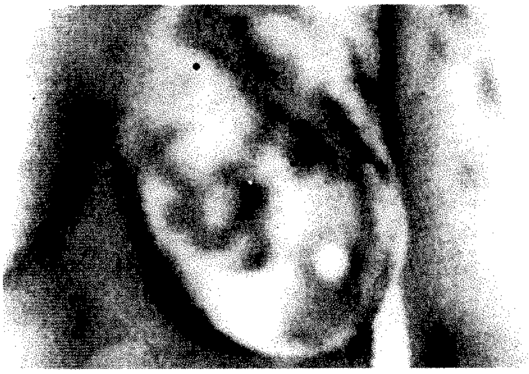

FIG. 2. Normal thermogram with prominent veins, anterior view of left breast.

darker than cool areas. Newspaper facsimile paper is used rather than Polaroid film (Fig. 1, *A* and *B*; and 2).

VENOUS DIAMETER RATIO

Dodd and Wallace[2] also devised a mammographic venous diameter ratio (VDR). This ratio is obtained in the absence of an obvious mass by measuring the diameter of the largest vein in either breast and comparing it with the diameter of the vein draining a comparable area in the opposite breast. If a mass is present, the largest vein in the vicinity of the mass is measured and compared with the opposite breast. Measurements are made by using a 7 power "eyepiece" magnifier* with a 20 mm. scale in 0.1 mm. divisions. The ratio of 1.4:1 was used as the arbitrary point above which the lesion was considered malignant and

* Bausch and Lomb.

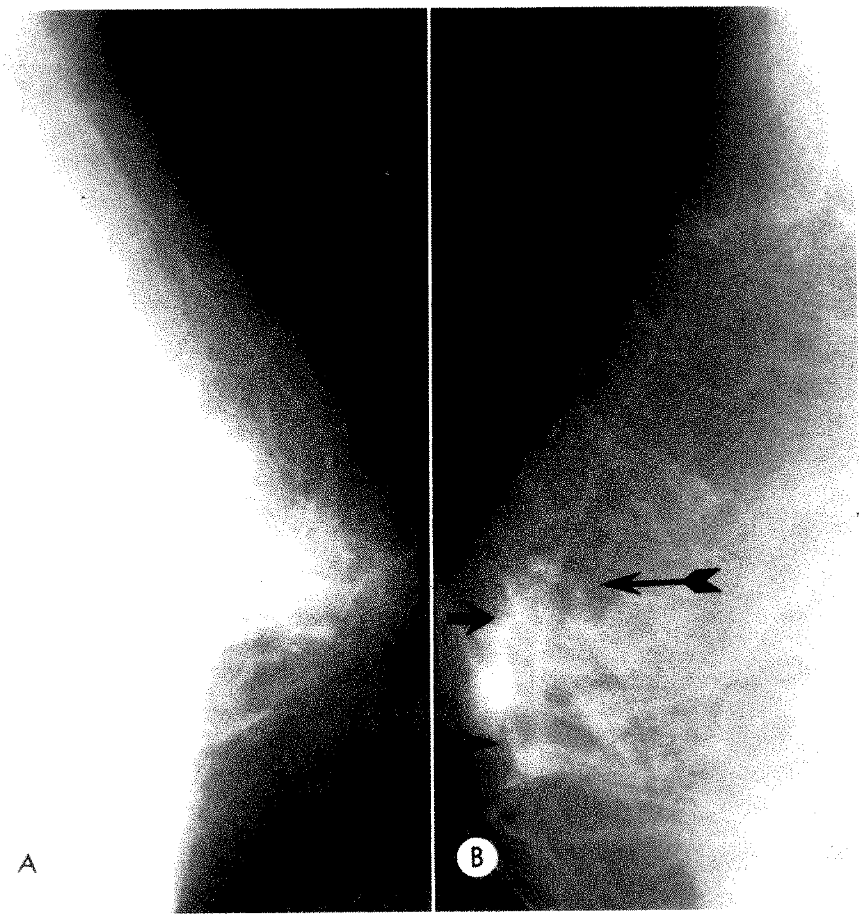

FIG. 3. Patient A.N. (*A*) Mammogram of right breast showing normal venous distribution. (*B*) Mammogram of left breast with a similar venous pattern but with a large vein in the nipple area (narrow arrows). The venous diameter ratio (VDR) using this vein was 1.5:1. Wide arrow indicates carcinoma.

below which, benign. A true positive rate of 75 per cent in 274 proven cases was found using *only* this parameter. The VDR may serve as not only the confirmatory measurement following a positive thermogram, but in the case of a very small carcinoma or one obscured by benign disease, it is of assistance in localizing a biopsy site (Fig. 3, *A* and *B*).

In the detection of the nonpalpable lesion the use of thermography and the venous diameter ratio as tandem procedures has been employed. All patients referred for mammography also have a breast thermogram. In the reading procedure the thermogram is scanned initially. The venous diameter ratio is then calculated, followed by the routine screening of the mammogram for mass lesions. In the presence of benign breast disease, in particular the premenopausal patient with dense breasts, a negative thermogram and a negative VDR are of great assistance in concluding that no malignancy is present. On the other hand, the radiologist is frequently alerted to the small, nonpalpable lesion by the presence of a positive thermogram and a high venous diameter ratio (Fig. 4, *A–E*). In three of our patients the positive thermogram and VDR indicated that a malignancy was present and these cases were later proven in the absence of either a palpable mass or a visible one on the original mammogram (Fig. 5, *A*, *B* and *C*). The detection of the nonpalpable lesion in the past has been for the most part dependent on the presence of calcification or upon the isolation of the lesion in a breast replaced by fat. The thermogram and VDR have led us to biopsy several positive cases, in which a lesion could not be clearly defined on the mammogram. Benign breast disease may obscure the borders of a small carcinoma, the presence of which is usually clearly signalled by a positive thermogram and high venous diameter ratio (Fig.6, *A–D*).

Occasionally a benign lesion will increase the vascularity causing a positive thermogram and venous diameter ratio. This type of lesion on biopsy has proven to be predominantly cystic ductal hyperplasia, sclerosing adenosis, a ductal papilloma or a fibroadenoma. Many benign lesions of the breast have been biopsied in the past on the grounds of physical examination alone. There is no question that many benign lesions are biopsied on the grounds of a mammography report. The thermogram and venous diameter ratio, however, can shift the emphasis from biopsies of fibrocystic breasts and other benign palpable lesions to biopsy of small lesions based on an increase in vascularity. Biopsy on the latter basis should yield a higher percentage of nonpalpable carcinomas. In the past year 6 nonpalpable carcinomas have been detected; none had evidence of axillary lymph node metastases.

Bilateral carcinoma presents a problem as the venous diameter ratios are often negative. We have collected a total of 21

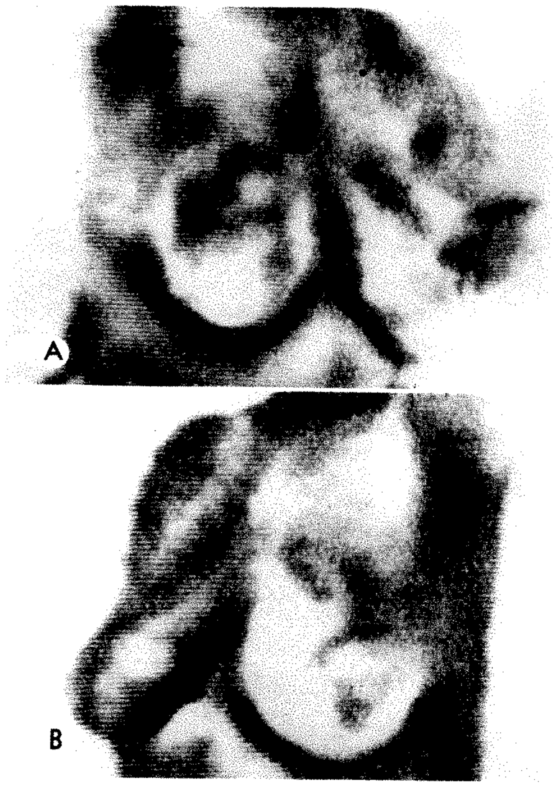

Fig. 4. Patient C.E. (*A*) Oblique thermogram of right breast showing large area of increased heat emanation. (*B*) Oblique thermogram of left breast showing normal venous distribution.

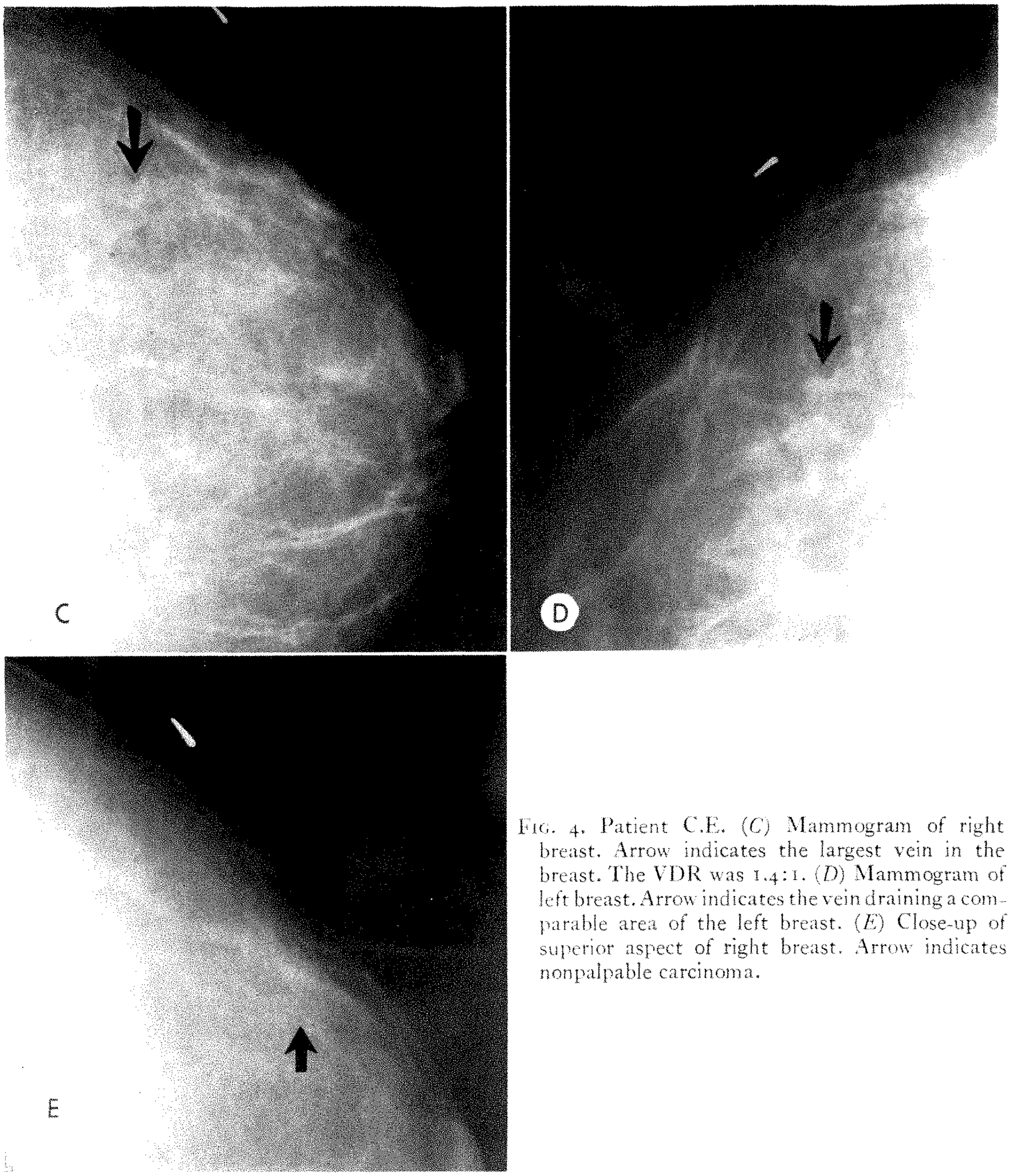

FIG. 4. Patient C.E. (*C*) Mammogram of right breast. Arrow indicates the largest vein in the breast. The VDR was 1.4:1. (*D*) Mammogram of left breast. Arrow indicates the vein draining a comparable area of the left breast. (*E*) Close-up of superior aspect of right breast. Arrow indicates nonpalpable carcinoma.

patients with nonpalpable carcinoma and 5 of these were bilateral; 4 were palpable on one side and 1 was not palpable on either side. Of the 16 unilateral nonpalpable carcinomas, 13 had positive venous diameter ratios and 15 positive thermograms.

A pilot study of an asymptomatic group of patients using thermography alone as a screening procedure has been initiated. In the case of a positive thermogram complete mammography is carried out. Four hundred and sixty-seven of these women have been screened to date and one nonpalpable carcinoma was detected. Several other carcinomas were also found in this group, but these were palpable.

mography in mass screening procedures for breast cancer.

The method is fast, economical and reliable for performing mammography with a minimal radiation dose. It is presented only as a screening procedure.

Suspicious cases can and should be checked with conventional mammography.

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ROENTGEN MANIFESTATIONS OF VAGINITIS EMPHYSEMATOSA

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VAGINITIS emphysematosa, a benign self-limiting condition involving the cervix and vagina, is characterized by the presence of gas-filled cysts beneath the epithelium of the cervix and vagina. While the physical appearance may be confusing, the roentgenologic characteristics are distinctive and the diagnosis, in many instances, may be readily made in this manner. We were alerted to the roentgenologic manifestation by Francke's[3] report in 1961. More recently, Whalen and Ziter[10] reported a second case. To these 2 previously reported instances, which established the roentgenologic characteristics, we present 4 additional cases.

REPORT OF CASES

CASE I. Mrs. M. S., a 41 year old gravida V, Para 3 Negro female was admitted to the hospital in early labor with vaginal spotting. It had been 16 years since her last pregnancy. Roentgenograms were obtained on admission (Fig. 1, *A* and *B*). After a 4 hour labor, she was delivered with low forceps, under a pudendal block anesthesia, of a full term female.

CASE II. Mrs. E. K., a 41 year old gravida IV, Para 3 white female was admitted to the hospital and delivered spontaneously, under general anesthesia, after a 6 hour and 40 minute labor. Roentgen studies had been obtained the day before admission because she was 1 month past EDC (Fig. 2, *A* and *B*).

CASE III. Mrs. C. H., a 31 year old gravida III, Para 1 white female delivered a full term male spontaneously under general anesthesia, after a 3 hour and 15 minute labor. Vaginal examination after delivery revealed bullae beneath the mucosa of the cervix and upper vagina. In the fornix these bullae resembled a cluster of varicosities. Several of the cystic spaces ruptured during labor (Fig. 3, *A* and *B*).

CASE IV. Mrs. I. H., a 28 year old gravida III, Para 1 white female had roentgenographic examination 1 month prior to delivery. Abdominal roentgenograms revealed collections of gas in the vagina. Direct examination confirmed

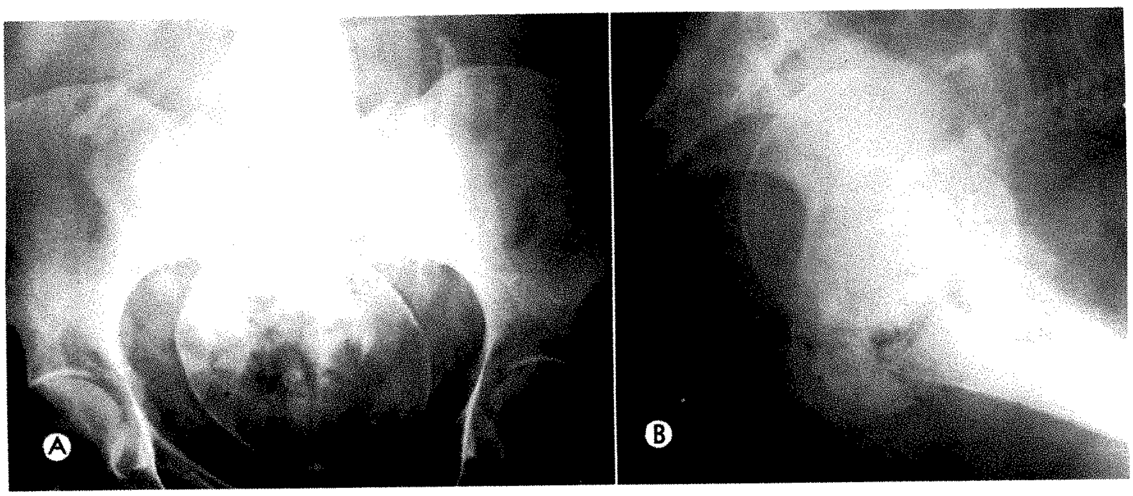

FIG. 1. Case I. (*A*) Anteroposterior roentgenogram showing numerous small, ovoid radiolucencies above and below the symphysis pubis. (*B*) Lateral view of pelvis demonstrates a long, thin, crescent shaped collection of gas below the engaged fetal head extending from the symphysis to the presacral region. Isolated cystic spaces are noted anteriorly.

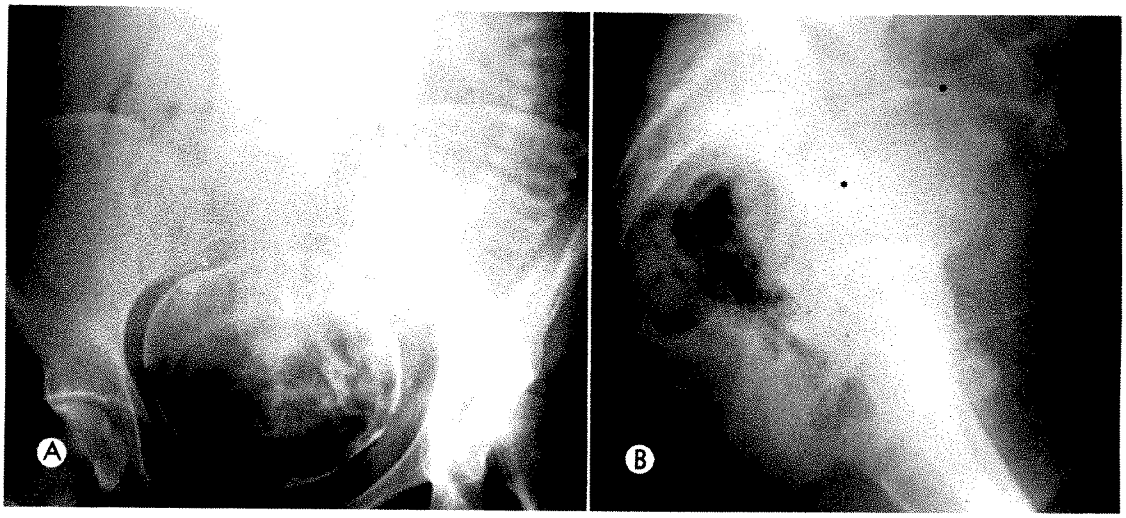

Fig. 2. Case II. (*A*) Anteroposterior roentgenogram shows a large aggregation of small gas-filled cysts above the symphysis. (*B*) In the lateral projection, cystic spaces are well demonstrated in the plane of the midpelvis.

the roentgen observation. Smears of vaginal secretions established the presence of *Trichomonas vaginalis* (Fig. 4, *A* and *B*).

DISCUSSION

Although all of our cases were associated with pregnancy, and while many instances of the abnormality previously reported were similarly associated, the lesion is not necessarily peculiar to the gravid state. Forty-three[4] instances were discovered at postmortem examination and a high percentage of these patients died of cardiovascular or respiratory ailments.

In 1964, Gardner and Fernet[4] reviewed the literature and collected 155 cases in which the diagnosis was made by physical examination, biopsy or autopsy. Classically, the gross appearance is characterized by tumor-like projections several millimeters to several centimeters in diameter and is confined largely to the cervix and

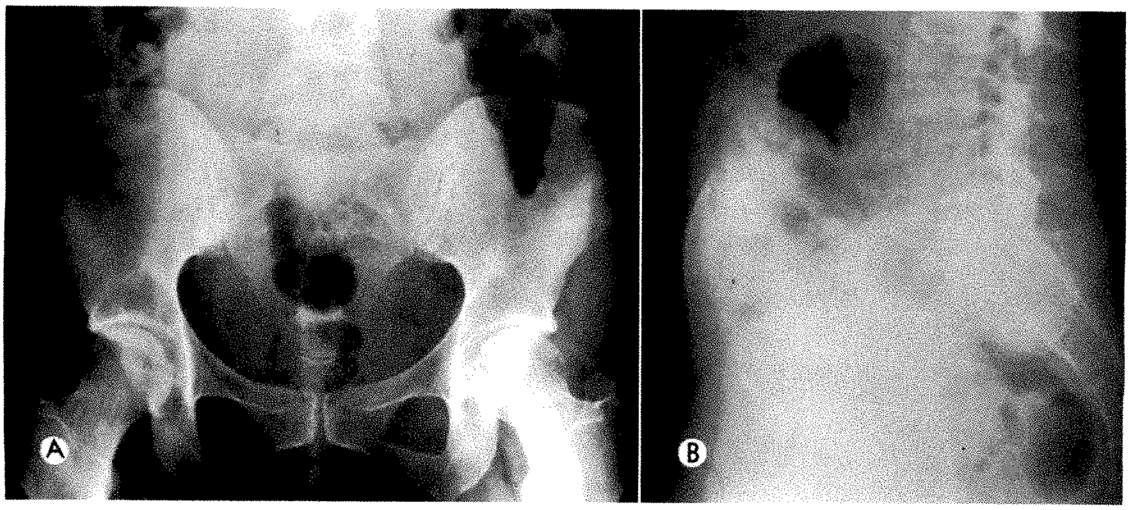

Fig. 3. Case III. (*A*) Anteroposterior view of the pelvis a few hours following delivery. A small collection of radiolucent shadows is observed above the symphysis. (*B*) In the lateral view, gas shadows are located in the central third of the midpelvic plane anterior to the rectum and well posterior to the symphysis.

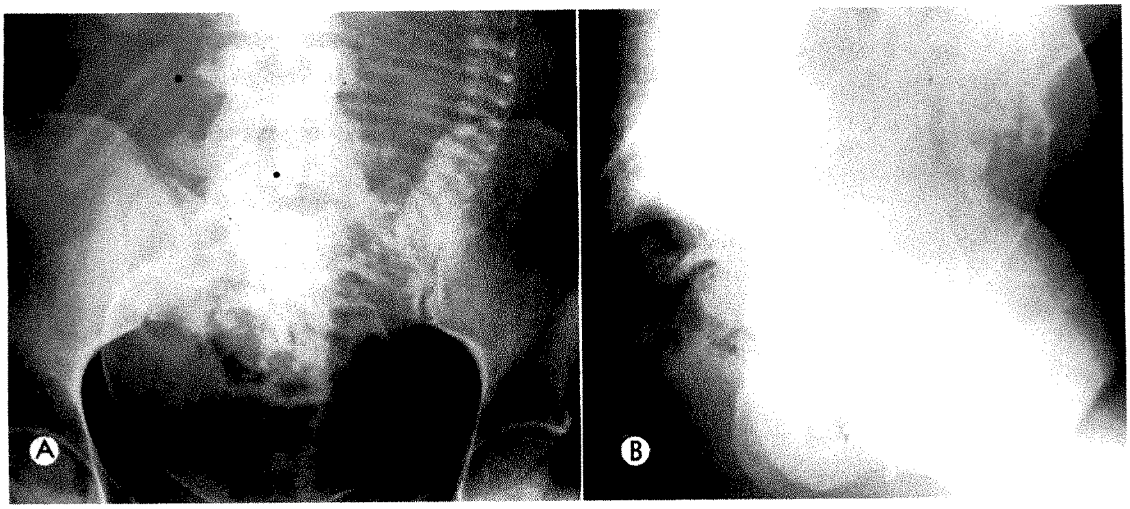

Fig. 4. Case iv. (*A*) Anteroposterior roentgenogram of the abdomen. Numerous small radiolucencies are seen immediately above the symphysis. (*B*) In the lateral view, areas of emphysema are again observed in the central one-third of the midpelvic plane.

upper two-thirds of the vagina. Gardner and Fernet[4] stated that the condition has been confused with practically every other lesion that can involve the vagina. As a rule, however, if the physician is aware of this entity, the diagnosis is fairly evident. Gardner and Fernet[4] emphasized that the presence of "granular vaginitis" should arouse the suspicion of vaginitis emphysematosa.

The outstanding microscopic feature consists of clear cystic spaces of varying size. These are often multiloculated throughout the subepithelial tissues. A syncytium of giant cells may line, or partially line, some of the cavities. Abell[1] stated that lesions thought to be of recent origin appear to be under tension and result in compression of the adjacent stroma. Very little cellular reaction is present in new lesions, while around the older lesions an accumulation of lymphocytes, mononuclear cells, and multinucleated giant cells may be seen. Hyperplasia of the squamous epithelium is commonly observed and may result in a pseudoepitheliomatous appearance. Dilated veins and lymphatics deep in the vaginal wall may be seen, and dilatation of the capillaries and venules immediately beneath the epithelium is also occasionally noted.

Ingraham and Hall[6] collected gas for analysis and found it to be 21 per cent oxygen by volume. Hoffman and Grundfest[5] found CO_2 to be 8–20 per cent by volume. Gardner and Fernet's[4] findings by spectrographic analysis were as follows: nitrogen 77.2 per cent, oxygen 20.8 per cent, argon 1.2 per cent; CO_2 was not identified. In our fourth case we attempted to aspirate gas for analysis, but were unsuccessful. The precise gas composition remains in doubt and may vary in different instances of the disease. Continued attempts at gas analysis should be encouraged for it is possible that several different pathogenetic mechanisms may be operative.

Several theories[4] have been advanced to explain the origin of the gas. One of the most attractive is that gas-forming organisms become entrapped in adherent vaginal folds. Another closely related theory is that the cysts originate from dilated lymph spaces infected by bacteria. A mechanical theory has also been suggested—atmospheric air being forced into the interstitial spaces of the vagina.

In the microbiologic investigations of

Gardner and Fernet,[4] *Trichomonas vaginalis* infection was found in 7 cases and *Hemophilus vaginalis* in 3. In our fourth case, *Trichomonas vaginalis* was present, and following control of the infection, the lesion disappeared. This is similar to Gardner and Fernet's experience.

In support of the proponents of the infection theory, Newton *et al.*[8] demonstrated the development of gas in the subcutaneous tissues in germ-free guinea pigs following the injection of a human strain of *Trichomonas vaginalis*. Gas analysis by means of a mass spectrometer revealed the presence of the usual blood gases in most instances. Twenty-six per cent hydrogen was found in one instance, however.

Pregnancy is thought to predispose to vaginitis emphysematosa because of development of increased vascularity, increased estrogen, and increased glycogen content. These changes, it is thought, may be of importance in creating an environment favorable to the growth of certain organisms. Why the lesion occurs in older individuals with cardiovascular and respiratory disease is even more uncertain.

The roentgen findings of vaginitis emphysematosa are characterized by an ovoid collection of varying-sized gas shadows over and above the symphysis. In the lateral projection they are grouped in a rectangular fashion in approximately the midsagittal plane at the midpelvic level. As the presenting part engages, the cystic spaces become more widely dispersed above the symphysis and, in the lateral projection, extend from the presacral area almost to the symphysis. In our Case 1, as a result of the deeply engaged head, a long sickle-shaped radiolucent shadow was observed below the fetal calvarium. Cystitis emphysematosa must be considered in the differential diagnosis and pyelography may be required to exclude it. Certainly, the radiologist is in a position to alert the gynecologist of the possible existence of this entity.

Roentgenographically, similar lesions are observed in pneumocholecystitis, cystitis emphysematosa, emphysematous gastritis, and pneumatosis intestinalis.[2] The clinical coincidence of diabetes mellitus and infection with gas-producing organisms, seems to be operative in the gallbladder and urinary bladder. The association of diabetes mellitus and vaginitis emphysematosa has been mentioned only once.[1] In both gross appearance and clinical behavior, pneumatosis intestinalis and vaginitis emphysematosa are more analogous than the other entities. Keyting *et al.*,[7] have shown that pneumatosis intestinalis may be associated with chronic pulmonary disease. In this instance, it is thought that air gains access to the mediastinum as a result of alveolar rupture, then enters the abdomen retroperitoneally, and finally reaches the bowel by angiomatous routes. In our opinion, isolated emphysema of the vagina would be difficult to explain by this mechanism. We point this out because pneumatosis intestinalis with vaginal involvement has been mentioned by two authors,[2,9] but in our search of the literature we have been unable to find either a well-documented clinical example or roentgenologic confirmation.

CONCLUSIONS

1. Vaginitis emphysematosa is a lesion which can be easily diagnosed roentgenographically.
2. Four cases are reported with positive roentgenographic findings. The first suspicion of the lesions was aroused by roentgen studies in 3 of our 4 cases.

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APPARATUS FOR CEREBRAL ANGIOGRAPHY*

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FOR the convenient performance of cerebral angiography, particularly by the femoral route, we have adapted and modified commercial equipment and added some that is new, borrowing ideas from many sources including the Department of Radiology at the University of Chicago. Our principal objectives were:

1. Provision of television fluoroscopy from the femoral region to the vertex without "blind spots."
2. Construction of a narrow, radiolucent headrest projecting from one end of a fluoroscopic tabletop so that the side of the head might be brought close to the surface of the vertical member of a pair of 10 inch by 12 inch Schönander cut film changers.
3. Ability to bring the full width of the tabletop over the frontal changer for the filming of other body parts (Fig. 5).
4. Arrangements for easily rotating the assembly of biplane film changers and attached x-ray tubes through 180° so that either the right side or the left side of the head may be brought close to the lateral film.
5. Possibility for the operator to work from either side of the fluoroscopic table.
6. A convenient means of elevating the patient's shoulders to put tension on the anterior surface of the neck when injection is to be made directly into neck vessels.

Major components are a modified Philips catheterization table and a pair of Schönander 10 inch by 12 inch cut film changers with associated frontal and lateral x-ray tubes, the changers and tube arms being mounted on a turntable which rests on a wheeled truck (hereafter referred to as the dolly) running on tracks anchored to the floor. New construction and modifications were done in the experimental shops of the University of Florida Medical Center by Mr. Charles Rabbit and other members of the staff of the shop director, Mr. Ovid R. Gano.*

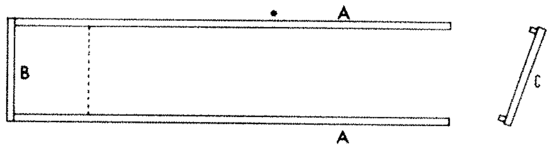

Fig. 1. Frame of tabletop. A. Side rails. B. End piece at foot of frame (retained). C. End piece at head end of frame (replaced by sheet magnesium).

CATHETERIZATION TABLE

As supplied by the manufacturer this table consists of a 20 1/2 inch by 89 inch radiolucent tabletop capable of movement laterally and longitudinally on a fixed base. The unmodified top is not suitable for cerebral angiography because it does not allow bringing the side of the patient's head into contact with the lateral film and if the image amplifier is placed inside the base, the patient's head and neck cannot be brought into the fluoroscopic field. The latter difficulty can be overcome by mounting the amplifier on a bracket protruding from the base (Fig. 3) and the former by providing a radiolucent headrest 12 inches wide and 15 inches long projecting from the end of the tabletop (Fig. 2).

TABLETOP

The simplest way to provide such a headrest would be to bolt one to the end of the otherwise unmodified top, but to do so would leave a fluoroscopic "blind spot" where the heavy steel end piece of the frame crosses the field of vision (Fig. 1). On the other hand, merely to remove this

* Those desiring them may obtain detailed mechanical drawings for a nominal charge by application to Mr. Ovid R. Gano, Bio-Electronica Shop, University of Florida Medical Center, Gainesville, Florida 32601.

* From the Department of Radiology, University of Florida, College of Medicine, Gainesville, Florida.

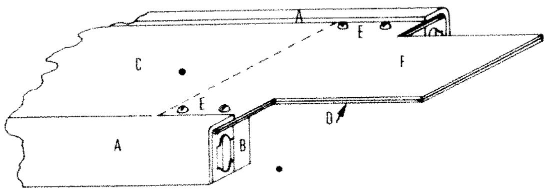

FIG. 2. Headrest and rails at head end of table. A. Side rails. B. Blocks bolted to ends of rails. C. Sheet plastic top. D. Sheet magnesium (1/16 inch) extending to dotted line. E. Machine screws anchoring plastic-magnesium sandwich to rails. F. Radiolucent headrest projecting beyond end of frame.

The arrangement provides a top of adequate strength in spite of the omission of the heavy steel end piece from the head end of the frame. Unlike the steel, the "sandwich" of magnesium cemented to plastic interposes little obstruction to the x-ray beam.

end piece would weaken the top to an unacceptable degree. We solved the dilemma in the following manner: The plastic top was removed from its frame and a sheet of strong but highly radiolucent magnesium was cemented to the under surface at one end. This magnesium is 1/16 inch thick, 19 inches wide and 24 inches long. When the cement had cured for 24 hours, 4 1/4 inch by 15 inch segments of the "sandwich" were sawed out at either corner leaving a median, tongue-like projection 12 inches wide and 15 inches long to serve as the headrest (Fig. 2). The steel end piece was removed from the head end of the frame (Fig. 1) and the top bolted back on to the side rails with the headrest projecting 15 inches beyond the end of the frame. This left a gap of 15 inches at the foot end of the top, a nonsensitive region which could be filled in with plastic cemented to sheet aluminum.

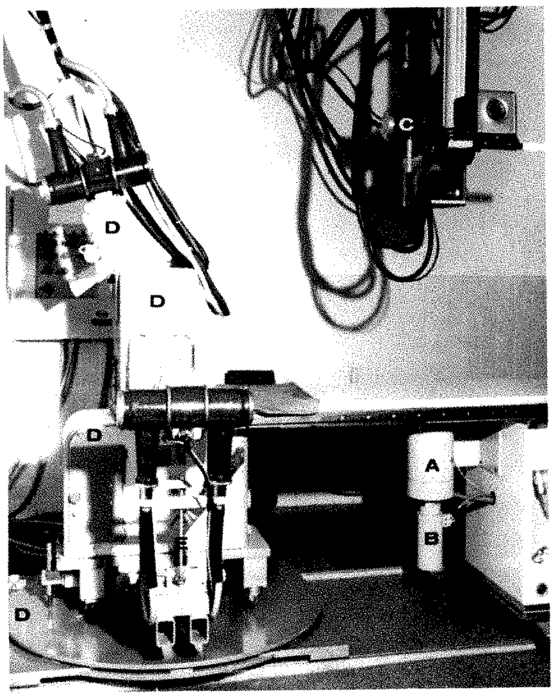

FIG. 3. Apparatus arranged for fluoroscopy of femoral region. A. Image amplifier on bracket attached to tablebase. B. Plumbicon T.V. tube. C. Ceiling mounted x-ray tube located directly above center of amplifier. D. Assembly of tube arms and film changers (shown in position for left cerebral angiography). E. Screw for occasional displacement of lateral x-ray beam above or below center of lateral film.

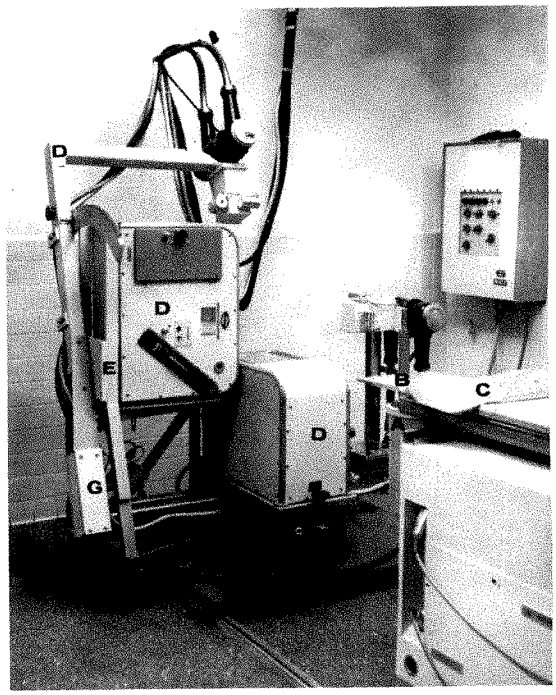

FIG. 4. Apparatus arranged for fluoroscopy of head (fluoroscopic tube not yet in position). A. Image amplifier directly beneath headrest. B. Headrest. C. Inflatable pad on which patient's shoulders will rest (not shown are motor-driven air compressor inside base and switch and air valve on far side of base). D. Assembly of tube arms and film changers in position for right sided angiography. E. Support for frontal tube arm. F. Support for lateral tube arm. G. Counter-weight for frontal tube arm.

When the top, thus modified, was reattached to its carriage on the base, it appeared to have the necessary rigidity, an impression which has been confirmed by several months of active clinical use.

TABLEBASE

A right angled bracket bolted to the head end of the base carries a Philips 5 inch image amplifier and a Plumbicon T. V. camera, the center of the amplifier window lying 2 1/4 inches below the under surface of the tabletop (Fig. 3). With the top displaced as far as it will go toward the foot end of the base and the patient's head centered on the headrest, the entire head is within the fluoroscopic field (Fig. 4), and with the top displaced as far as it will go in the opposite direction, the field of fluoroscopic vision extends beyond the femoral region (Fig. 3). If one looks critically, he can see that the brilliance of the fluoroscopic image is slightly greater where radiation passes through the plastic top alone, and slightly lower where magnesium is interposed as well; however, the difference is so small that it can be easily overlooked and is of no clinical significance.

AIR CUSHION TO ELEVATE SHOULDERS

Within the base, in place of the image amplifier, we have mounted a small electrically operated air compressor intended for spraying paint. Air from the compressor passes through rubber tubing to a pneumatic cushion designed by Mr. Anthony Konopka, R.T. and supplied commercially by the Hogan X-ray Company of Philadelphia. The deflated cushion lies beneath the patient's shoulders (Fig. 4) and when it is necessary to raise his shoulders, the operator closes a relief valve on the hose line and operates the compressor motor until the desired degree of cushion inflation has been reached. To deflate the cushion, he opens the relief valve.

X-RAY TUBES

Three x-ray tubes are employed. One of them, carried on a conventional ceiling tube crane, is used for fluoroscopy (Fig. 3)

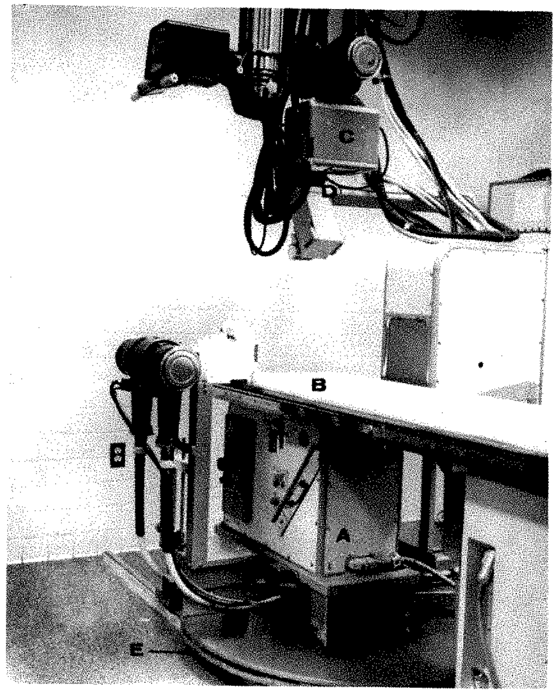

Fig. 5. Apparatus arranged for thoracic aortography. A. Frontal changer shifted 6 1/2 inches laterally to allow bringing full width of tabletop over frontal film. B. Tabletop positioned over frontal film changer. C. Ceiling-mounted tube shifted from fluoroscopic to filming position. D. Rigid frontal tube arm angled out of the way. E. Ear-like protrusions (one at either side of the dolly) to carry 2 of the 8 roller bearings on which turntable rides.

and for the occasional making of thoracic aortograms in connection with cerebral angiography. (It is used also for pneumoencephalograms with a special chair not shown here.) The other two x-ray tubes, mounted on rigid arms incorporated in the film changer assembly, are used for taking frontal and lateral cerebral angiograms (Fig. 6).

When the operator moves the fluoroscopic tube into position directly over the image amplifier, magnetic latches hold it in that position and with the frontal control stand set at "fluoroscopy," the tube operates at 1.5 ma. and 80 kv. when a foot switch is closed.

For the special situation of thoracic aortography, this tube is moved from its fluoroscopic position to a point directly above the center of the (laterally displaced) frontal film changer and it, rather than the

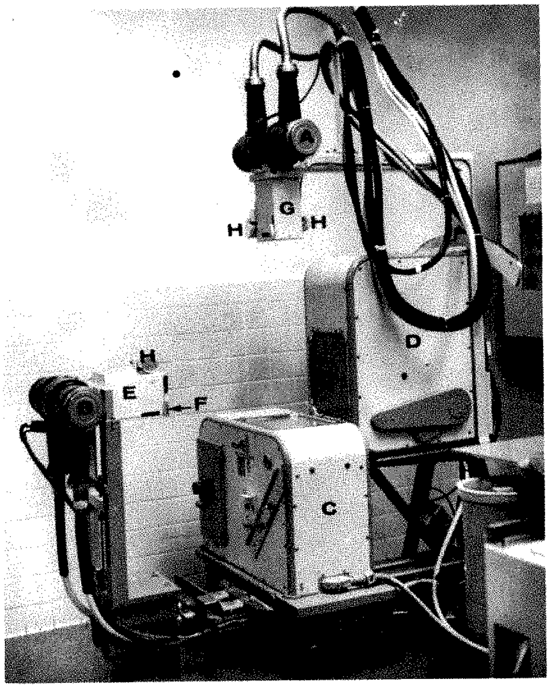

Fig. 6. Apparatus arranged for left sided angiography. A. Frontal x-ray tube. (Arms shown with frontal beam at 90° to frontal film. By means of a pivot, lying in the plane of the frontal film, the beam may be angled in either direction away from the perpendicular.) B. Lateral tube with its beam centered at center of lateral film (it may be shifted slightly above or below center). C. Frontal changer (shown in its normal position in contact with lateral changer). D. Lateral changer. E. Beam collimator on lateral tube. F. Lever for operation of 5 inch by 5 inch stop. G. Collimator on frontal tube. H. Light localizers. (They cast bright cross marks defining centers of the two beams.) I. Transformers supplying 6 volts A.C. to localizer lamps.

regular frontal tube, is placed in circuit by the programmer (Fig. 5). The reason for the substitution of tubes and the means of accomplishing it are explained later in this article.

ASSEMBLY OF FRONTAL AND LATERAL SCHÖNANDER CUT FILM CHANGERS

The two film changers and associated programmer are of the electronically synchronized type which allows making frontal and lateral roentgenograms at a single injection of contrast medium with a minimum of cross fogging. This makes it possible to use linear rather than cross hatched grids, thus allowing angulation of the frontal beam for certain views and, in some instances, the centering of the lateral beam above or below the center of the film. The manufacturer supplies a tripod stand for the lateral changer and the frontal changer has casters so that it can be rolled along the floor and arranged with one side close to the plane of the lateral film. For both changers, free standing (or free hanging) x-ray tubes usually are used. We have modified the tripod, somewhat in the manner used at the University of Chicago, tying the two changers together and providing supports (Fig. 4) for special tube stands presently to be described (Fig. 6). For cerebral angiography the longitudinal axis of the frontal film lies 7 inches away from the plane of the lateral film. When the frontal beam is to be directed at 90° the transverse axis of the frontal film coincides with the longitudinal axis of the lateral film, but when the beam is angled away from the perpendicular, the transverse axis of the frontal film is displaced 1 1/2 inches in the appropriate direction to correct for image drift (Fig. 7).

In thoracic aortography only the frontal changer is used and it must be moved 6 1/2 inches away from the lateral changer (Fig. 5) to allow room for bringing the full width of the tabletop into position over the frontal film. When this has been done a micro switch, activated by the base of the changer, switches programmer and control circuits to the ceiling-mounted x-ray tube.

SPECIAL TUBE STANDS

Substantial brackets attached to the tripod for the frontal changer carry the frontal and lateral x-ray tubes (Fig. 4). In both instances target-film distance is fixed at 36 inches and rectangular collimators measuring $4\times5\times8$ inches define 10 inch by 12 inch fields on the two films. Stops held in place by magnetic latches may be used to further restrict fields to 5×5 inches. Two pairs of modified Schönander light localizers cast bright cross marks

indicating the centers of the frontal and lateral x-ray beams. The lateral beam normally is fixed at the center of the lateral film but by means of screw adjustment it may be elevated above or below that center. The frontal beam is centered at the longitudinal axis of the frontal film and may be angulated from the 90° position toward the head or toward the feet until the angle is as small as 65° (usually not less than 75°). The axis of rotation of the frontal tube arm lies exactly at the plane of the frontal film. When the frontal beam is at 90°, the frontal changer is used in its central position. When the beam is angled away from 90° the changer is shifted 1 1/2 inches in the appropriate direction.

DOLLY AND TURNTABLE

The assembly of tripod, frontal and lateral changers and frontal and lateral tube stands is bolted to a sheet aluminum disk 5/8 inches thick and 48 inches in diameter. This disk serves as a turntable turning on an aluminum dolly, 5/8 inches thick, 48 inches long and 40 inches wide with ear-like circular segments enlarging the width at the center to 48 inches (Fig. 5).

A 1 inch steel shaft, rising from the center of the dolly, passes through a brass bearing at the center of the disk and 8 roller bearings, equally spaced near the edge of the dolly, carry the weight of the disk-changer-tube-stand assembly.

Six additional roller bearings serve as wheels for movement of the dolly toward or away from the table on tracks attached to the floor. Nineteen inches of dolly movement is possible and a manual lock is provided to fix the dolly when the desired position has been reached (Fig. 8).

The turntable may be rotated through 180° and locked at either end of such rotation. High voltage and low voltage cables for tube and changer circuits are brought through the ceiling at a point close to the center of the turntable rotation, so that rotating the assembly from the position for a right sided angiogram to that for a left sided examination causes a minimum of twist and tension of cables.

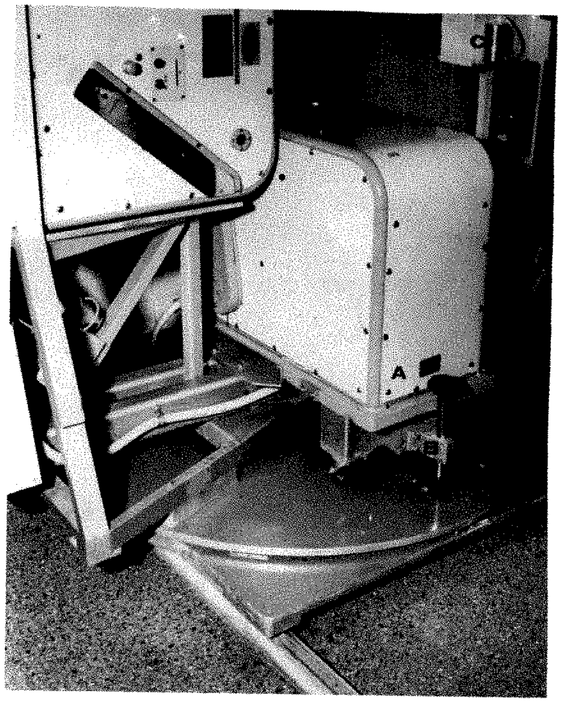

Fig. 7. Details of changers, turntable and dolly (frontal beam angled 75° toward feet). A. Frontal changer. (This is shifted 1 1/2 inches below central position to compensate for image drift incident to angulation of frontal beam.) B. Lock for frontal changer. (There are 3 tapped holes in the disk to receive the changer lock. With lock in central hole, transverse axis of frontal film is aligned with longitudinal axis of the lateral. As shown here, with lock in lower hole, the transverse axis of the frontal is displaced 1 1/2 inches below the longitudinal axis of the lateral.) C. One of the two light localizers on the lateral collimator.

EXAMPLES OF CLINICAL APPLICATION

LEFT CAROTID ARTERIOGRAPHY BY FEMORAL ROUTE

The turntable is rotated so that the plane of the lateral film will be at the left side of the patient's head and locked in that position. The dolly is moved away from the table to the end of its travel and the ceiling mounted x-ray tube is locked in position directly above the center of the image amplifier (Fig. 3).

The patient is placed, back down, on the table with his head centered on the head-

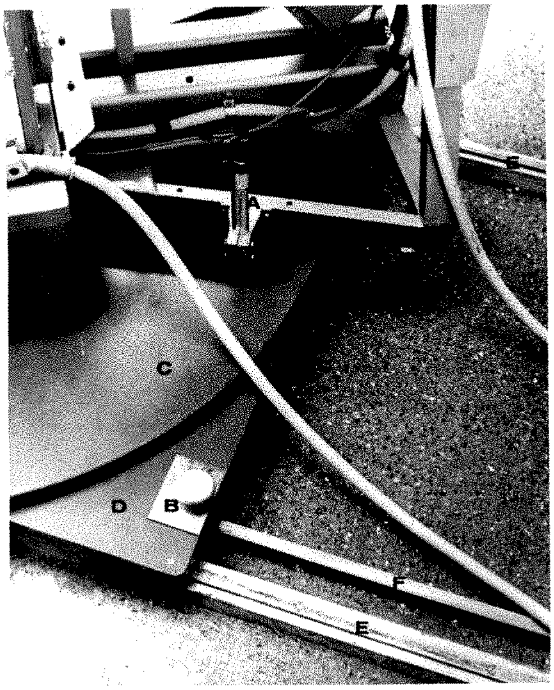

FIG. 8. Locks for turntable and dolly. A. Turntable lock. (In this view the disk is in intermediate position to facilitate work of photographer making the exposure for this figure. In practice, turntable is rotated into full right or full left position and locked there by threading stem of lock into tapped hole in dolly beneath a drilled port in the disk.) B. Dolly lock. (When the lock is screwed down, a neoprene covered clamp grips the metal strip locking the dolly at any desired point along its 19 inches of travel.) C. Disk of turntable. D. Wheeled dolly running on track. E. Track. F. Metal strip for dolly lock.

rest and the tabletop shifted until the femoral region is in the fluoroscopic field. As a catheter is passed up through the abdominal and thoracic aorta, the tabletop is shifted again and again to keep the catheter tip in the field, the process being continued (sometimes with very small test injections) until the tip has been lodged in the desired neck vessel.

Meanwhile the magazines of the changers have been loaded and the frontal tube-arm located at the desired angle following which the tabletop is shifted to the end of its travel bringing the center of the headrest over the center of the frontal film (or 1 1/2 inches above the center if the radiation is to be angled toward the patient's feet). By means of the light localizers final adjustment of the head is made after which the tabletop is drawn back long enough to allow application of immobilizing straps and then relocated in its former position relative to the two x-ray beams.

Turning on the Schönander programmer automatically puts the overhead fluoroscopic tube out of circuit and brings the two rigidly mounted tubes into circuit ready for biplane filming as soon as the injection has been made.

When carotid injection is to be made by needle, directly into neck vessels, usually fluoroscopy is not employed, but if desired it may be used for test injections.

THORACIC AORTOGRAPHY

The frontal film changer is moved 6 1/2 inches laterally from its normal position (Fig. 5) thus activating a microswitch which puts the ceiling mounted tube in the programmer circuit rather than the tube carried by the rigid arm. Until the programmer is turned on, the ceiling tube is used for fluoroscopy (Fig. 3), but when that has been completed and the programmer is turned on, the ceiling tube takes over frontal filming. (The lateral tube and changer are not used for this work.) The ceiling tube must be moved by hand from its former position above the image amplifier to a point directly over the center of the frontal film. When all this has been done, the tabletop is shifted laterally so that its full width clears the front of the lateral changer and then shifted longitudinally until the desired part of the patient's chest is centered in the field of radiation.

This substitution of a ceiling mounted x-ray tube for a rigidly mounted tube avoids the much more massive construction which would be necessary if the rigid tube had a screw adjustment allowing it to be moved 6 1/2 inches farther away from its supporting arm. Since we have other facilities for general aortography and the examination is needed only occasionally in connection with cerebral angiography, this

substitution of tubes, although somewhat clumsy, proves to be a practical expedient.

SUMMARY

An apparatus is described for the convenient performance of cerebral angiography. The clinical application of this equipment in the taking of left carotid arteriograms and thoracic aortograms is also discussed.

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The Fiftieth Annual Meeting of the Society will be held at the Hotel Fontainebleau in Miami Beach, Fla., April 7–11, 1968.

EDITORIAL

REGIONAL MEDICAL PROGRAMS

An Opportunity for Cooperative Effort

THE development of regional medical programs presents a particular opportunity for radiologists. With the continued rapid increase in science and medical knowledge, specialization within disciplines has been increasing. Furthermore, the incidence of certain diseases or the need for specialized equipment and information to undertake particular studies may be of such a magnitude that a concentration of effort would bring forth improved patient care. In the "Report to the President—Volume II," the Commission on Heart Disease, Cancer and Stroke stated that a 1961 survey "in the United States showed that 60 per cent of hospitals equipped with cardiac catheterization facilities performed fewer than 50 catheterizations per year; 79 per cent of those with angiocardiographic facilities did fewer than 50 angiocardiograms per year; and 77 per cent of all hospitals equipped for open-heart surgery performed fewer than 50 open-heart operations per year. Many hospitals did not use their facilities at all." Apart from the obvious increase in the cost of medical care which the inadequate use of equipment and space engenders, the radiologic discipline includes some procedures and techniques which would be better executed if centralized to a greater or lesser degree. Although anyone's list for what should be centralized for the benefit of the patient would vary, it might include in the field of nuclear medicine those procedures which require one of the rapid-scanning devices such as a gamma ray counter. In the same field, certain studies require computer coupling to the scanning device to be used in procedures such as comparing inhalation lung scans with perfusion lung scans.

Concentration of radiotherapy patients into relatively few centers has long seemed a desirable device to reduce costs, increase physician experience, and at the same time make available for the patient more sophisticated equipment than is usually available in modest supervoltage installations. This would include beams of megavoltage energy with improved field definition. A large penumbra on a machine used for rotation therapy can negate the advantages of high energy as compared with an orthovoltage unit. Electron beam therapy and equipment providing unusual motions or field controls are required perhaps by 10 to 15 per cent of all therapy patients. These advantages, however, can be provided with some centralized center planning.

The over-proliferation of angiographic facilities has already been documented as mentioned above. In diagnostic radiology, therefore, a list for centralization of facilities could be those related to selective coronary angiography and other selective arterial procedures for diagnosis or organ-localized drug therapy. Hypocycloidal motion was believed to be demonstrably advantageous according to the diagnostic radiologists polled in 10 to 30 per cent of those examinations requiring laminagraphy. And then, there are a host of procedures which cannot be classified as adroitly as the examples mentioned which are uncommon and which would best be performed by a diagnostic radiologist who would have the opportunity of retaining his skill because of the referral of all appropriate

patients from a relatively wide area. The ability of a particular radiologist to remain expert when dealing with diseases of low incidence or in executing procedures infrequently required in a population, is dependent on a sufficient amount of unusual case material coming into his view. The problem of maintaining excellence under the restriction of a low case load is not limited to certain aspects of our specialty. Furthermore, with the type of procedures alluded to above, not only must the particular radiologist be specialized and therefore relatively rare, but his paramedical support is equally specialized and rare.

How does one select in which city and in which hospital special procedure units are to be established? One can start by saying that the university medical center is a natural base as the regional hospital to which the selected hospitals will be related as associated centers. The incidence of diseases which are subject to hospital center care can be determined and correlated with the city and town of origin. Projections of population growth in any region can help in the selection of the site for the associated centers by favoring those areas predicted to have the greatest population density in 10 and 20 years. From appropriate state planning agencies, the projected major highways can be obtained and related to the centers of population growth, and towns of origin of the particular diseases. In the case of a "tie" between the towns, or two hospitals in a town, the hospital with the most diversified supporting staff or the hospital which for whatever reason appears to be economically favored should be selected. Topography must be taken into account as certain parts of a region might be relatively isolated and special provisions would be appropriate for this portion of the area; the minimum case load an associated and a regional center must see to sustain expertise and to warrant an expensive highly specialized facility must also be considered in evolving an ideal plan. Finally, the existing facilities and talents in the various cities and hospitals of the region must be utilized as much as possible in the final selection of centers.

In such an integrated regional medical plan, the university regional center hospital could actively participate in staffing the special procedure effort in the associated centers. To do this effectively, the radiologist spending the majority of his time in the associated center would spend at least one day a week at the university center at which time the work at the associated hospital would be covered by a different attending radiologist from the regional center. To maintain the doctor-patient relationship, patients referred to the regional university center would be scheduled for a first visit during the day when the radiologist from the associated center referring the patient would be at the university hospital. Furthermore, at regular intervals, radiologists at the associated center would visit the other hospitals in his referral area for clinics, lectures, or demonstrations in those subjects in which he is expert. These programs could act as a nidus for the addition of non-radiologic specialists from the associated centers or the regional university center to join with the radiologist in a continuing postgraduate educational program at each of the local hospitals.

One other important condition would have to be met, in the author's opinion, if the local doctor and his community hospital were to refer patients to the regional center and its associated centers. A major deterrent to physicians and a major inhibition of patients' acceptance of the concentration of certain medical activities in a few hospitals in a region is the fear of loss of contact between the local physician (radiologist) and his patient. For this reason, I would suggest that whenever a patient from a community hospital is referred to an associated or regional hospital with particular facilities the referring physician automatically should have courtesy privileges for visits to his patient in that hospi-

tal where the procedures or treatments are being undertaken.

In summary, I believe that in each of the subspecialties of radiology—diagnostic roentgenology, nuclear medicine, and radiation therapy—there are certain aspects of patient care which by their nature seem to demand concentration in a relatively few hospitals associated with a regional university center. Such organization for service to patients with problems of relatively low incidence will lead to improved medical care. However, to ensure acceptance of this principle by the public and their physicians, the referring physician or radiologist must be privileged to participate in the patient's care. While the referral of these particular patients would be centripetal, the referring physician (radiologist) must have courtesy privileges with respect to his patients in those associated hospitals, including the regional university center where the particular technique is practiced. Continuing education related to the specialist practice of the regional university and its associated hospitals would be centrifugal so as to reach all physicians and hospitals in the region served.

Morton M. Kligerman, M.D.
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NEWS ITEMS

THE AMERICAN COLLEGE OF RADIOLOGY

The Forty-fourth Annual Meeting of the American College of Radiology was held at the Drake Hotel, Chicago, Illinois, from Tuesday, February 6 to Saturday, February 10, 1968.

The following officers were elected: *President*, Joseph D. Calhoun, M.D., Little Rock, Arkansas; *Vice-President*, Homer V. Hartzell, M.D., Seattle, Washington; *Secretary-Treasurer*, Fay H. Squire, M.D., Chicago, Illinois (re-elected); *Chairman, Board of Chancellors*, J. Frank Walker, M.D., Atlanta, Georgia; *Vice-Chairman, Board of Chancellors*, Robert W. McConnel, M.D., Dallas, Texas.

On Wednesday evening the College had a joint dinner meeting in the Gold Coast room of the Drake Hotel, with the ACR and Illinois Chapter, Chicago Roentgen Society, at which Dr. Milford O. Rouse, President of the American Medical Association, was the speaker.

The College Fellowship Convocation was held Friday at 5:30 P.M., with Dr. J. E. Miller, President of the American College of Radiology, presiding. The degree of Fellow of the American College of Radiology was conferred on 87 candidates and the Degree of Associate Fellow on 2 candidates who have been approved by the Board of Chancellors and elected to fellowship by a vote of the Fellows.

The degree of Honorary Fellow was accorded to 10 outstanding radiologists of international renown.

As already reported in the March issue of this Journal, the awards to the 3 Latin American radiologists were made in a Special Convocation of the College, on the occasion of the Ninth Inter-American Congress of Radiology, held December 6–12, 1967 in Punta del Este, Uruguay. At this ceremonial convocation Dr. Fay H. Squire officiated as President of the College, Dr. J. E. Miller as Chairman of the Board of Chancellors, Dr. J. A. del Regato as Secretary and Dr. W. T. Snow as Sargent-at-Arms. The candidates honored were: Dr. Leandro Zubiaurre, Professor of Radiology of the University of Montevideo, Uruguay; Dr. Raúl Leborgne of Montevideo, Uruguay for his long and fruitful work in mammography; and Dr. Manuel G. Zariquiey of Rochester, New York, International Coordinator of the Eastman Kodak Company's Radiography Market Division, for his devotion to Inter-American Activities in Radiology.

At the Chicago ceremonies the degree of Honorary Fellow was awarded to: Dr. Leonidas Stergiou, Athens, Greece; and *in absentia* to: Dr. Hans H. Berg, Hamburg, Germany; Dr. Arduino Ratti, Milano, Italy; Dr. Lan Chang Chiang, Taipei, Taiwan; Dr. Sjahriar Rasad, Djakarta, Indonesia; and Dr. Joseph Rösch, Prague, Czechoslovakia.

Gold Medals, the highest award of the American College of Radiology "for distinguished service to radiology" were presented by President Miller assisted by Dr. Calhoun, Chairman of the Board of Chancellors to: Dr. Wallace D. Buchanan, Fort Wayne, Indiana; Dr. Juan A. del Regato, Colorado Springs, Colorado; and Dr. Russell H. Morgan, Baltimore, Maryland.

The agenda of the Friday morning meeting comprised presentation of the reports of Officers, Commissions and Committees followed (for the first time) by 4 Section Meetings. These were: (1) General Section, John R. Danstrom, M.D., Moderator; (2) Nuclear Medicine, E. Richard King, M.D., Moderator; (3) Pediatric Radiology, John L. Gwinn, M.D., Moderator; and (4) Radiation Therapy, Juan A. del Regato, M.D., Moderator.

On Saturday the always stimulating annual conference of Teachers of Radiology took place with Dr. Benjamin Felson, Cincinnati, Ohio, presiding.

The Forty-fifth Annual Meeting of the American College of Radiology will be held at the Regency Hyatt House, Atlanta, Georgia, February 18–22, 1969.

ELEVENTH ANNUAL W. EDWARD CHAMBERLAIN LECTURE

The Eleventh Lecture Correlating Radiology and Physiology, in the series honoring Dr. W. Edward Chamberlain, Emeritus Professor of Radiology, will be given by Dr. Earl R. Miller, Professor of Radiology, University of California, San Francisco Medical Center, on May 1, 1968 at 4:00 P.M. in the Auditorium of the Temple University School of Medicine, 3400 North Broad Street, Philadelphia, Pennsylvania.

The title of Dr. Miller's lecture is, "Continence and Voiding."

WASHINGTON UNIVERSITY SCHOOL OF MEDICINE

A Doppler ultrasound symposium will be given on May 23 and 24, 1968 at the Mallinckrodt Institute of Radiology, St Louis, Missouri, under the direction of Ray A. Brinker, M.D.

The Guest Faculty will include Dr. Donald W. Baker, Seattle, Washington; Dr. Ross E. Brown, Winnipeg, Manitoba, Canada; Dr. Dean Franklin, LaJolla, California; Dr. Bernard Sigel, Philadelphia, Pennsylvania; Dr. H. F. Stegall, San Antonio, Texas; and Dr. D. E. Strandness, Jr., Seattle, Washington.

The Symposium will cover the theoretical, practical and engineering considerations of Doppler ultrasound in diagnostic medicine. Specific lectures will be given on the monitoring, peripheral arterial and venous disease and carotid artery stenosis.

Inquiries should be addressed to Ray. A. Brinker, M.D., Mallinckrodt Institute of Radiology, 510 South Kingshighway, St. Louis, Missouri 63110.

THE TENTH INTERNATIONAL CANCER CONGRESS

FIRST CIRCULAR

The Tenth International Cancer Congress, with four preliminary Special Sessions, will be held in Houston under the auspices of the Unio Internationalis Contra Cancrum (U.I.C.C.), May 22–29, 1970.

The Scientific Program of the Congress is being prepared by the joint effort of the U.I.C.C. Committee on International Congresses and the USA National Organizing Committee.

The First Circular provides a preliminary outline of the Congress. More detailed information will be provided at a later date.

Application forms for travel, tours and hotel accommodations will be sent with Application Form for Registration in the Second Circular, to be issued in June, 1968.

The Chairman of the Congress is R. Lee Clark, M.D., and the Secretary-General, Murray M. Copeland, M.D.

For further information please write to: National Organizing Committee, Secretariat, The University of Texas, M. D. Anderson Hospital and Tumor Institute at Houston, 6723 Bertner Avenue, P.O. Box 20465, Astrodome Station, Houston, Texas 77025, Cable Address: CANCONG, Houston, Texas.

SOUTHERN RADIOLOGICAL CONFERENCE

At the Twelfth Annual meeting of the Southern Radiological Conference at the Grand Hotel, Point Clear, Alabama, the following new officers were elected: *Chairman*, Dr. Howard Barnhard, Chief, Department of Radiology, University of Arkansas School of Medicine, Little Rock, Arkansas; *Vice-Chairman*, Dr. Buell C. Buchtel, Foundation Hospital, 1516 Jefferson Highway, New Orleans, Louisiana; *Secretary-Treasurer*, Dr. Marshall Eskridge, Mobile Infirmary, P.O. Box 4097, Mobile, Alabama 36604.

The Thirteenth Annual meeting will be held at the Grand Hotel, Point Clear, Alabama 36564, January 31, February 1, and 2, 1969.

BOOKS RECEIVED

ent for review are acknowledged under: Books Received. This must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interest of our readers as space permits.

BOOKS RECEIVED

Dynamic Factors in Roentgen Diagnosis. By Elliott C. Lasser, B.S., M.D., M.S. (Radiology), Professor and Chairman, Department of Radiology, University of Pittsburgh School of Medicine; Director, Department of Radiology, Presbyterian-University Hospital; with a chapter by John H. Feist, M.D., and a foreword by Leo G. Rigler, M.D. Cloth. Pp. 356, with many illustrations. Price, \$12.75. The Williams & Wilkins Company, 428 E. Preston St., Baltimore, Md. 21202, 1967.

International Symposium: Enzymatic Aspects of Metabolic Regulation. Held at Mexico City, Mexico, Nov. 28–Dec. 1, 1966. Edited by M. P. Stulburg. National Cancer Institute Monograph 27, Nov. 1967. Cloth. Pp. 344, with many figures. Price, \$3.25. Superintendent of Documents, U. S. Government Printing Office, Washington, D. C. 20402, 1967.

Roentgenographic Diagnosis of Bladder Tumors. By Erich K. Lang, M.D., Radiologist, Methodist Hospital, Indianapolis, Ind.; Formerly, Associate Radiologist, Johns Hopkins Hospital, Baltimore, Md. Cloth. Pp. 120, with many illustrations. Price, \$9.75. Charles C Thomas, Publisher, 301–327 East Lawrence Avenue, Springfield, Ill. 62703, 1967.

Atlas of Roentgenographic Positions. By Vinita Merrill. Third edition. In 3 volumes. Cloth. Total pages, 878, plus index, with many illustrations. Price, \$46.50. C. V. Mosby Company, 3207 Washington Boulevard, St. Louis, Mo. 63103, 1967.

Das Mycetom. By Prof. Dr. Kurt Reinhardt, Chefarzt der Röntgenabteilung am Kreiskrankenhaus Völkingen/Saar. Paper. Pp. 120, with 16 figures. Price, DM 38.–. Ferdinand Enke Verlag, Hasenbergsteige 3, Stuttgart W, Germany, 1967.

Myelography. Second edition. By Robert Shapiro, M.D., Chairman, Department of Radiology, The Hospital of St. Raphael, New Haven, Conn.; Clinical Professor of Radiology, Yale University School of Medicine. Cloth. Pp. 440, with 455 illustrations. Price, \$24.00. Year Book Medical Publishers, Inc., 35 East Wacker Drive, Chicago, Ill. 60601, 1968.

Frontiers of Radiation Therapy and Oncology. Proceedings of the First Annual San Francisco Cancer Symposium. Volume I. Hyperbaric Oxygen and Radiation Therapy of Cancer. Edited by Jerome M. Vaeth, San Francisco, Calif. Cloth. Pp. 200, with 68 figures. Price, \$12.50. S. Karger AG., Basel. In the U.S.A., Albert J. Phiebig, P.O. Box 352, White Plains, N. Y. 10602, 1968.

Lehrbuch der Röntgendiagnostik: In fünf Bänden. Edited by Prof. Dr. med. H. R. Schinz; Prof. Dr. med. W. E. Baensch, Washington; Prof. Dr. med. W. Frommhold, Berlin; Prof. Dr. med. R. Glauner, Stuttgart; Prof. Dr. med. E. Uehlinger, Zürich; and Prof. Dr. med. J. Wellauer, Zürich. Band IV/Teil 1; Herz and grosse Gefässe. By J. Lissner, Frankfurt/M.; N. Schad, Zürich; P. Thurn, Bonn; and J. Wellauer, Zürich. Cloth. Pp. 568, with 1353 figures. Price, DM 224.–. Georg Thieme Verlag, Stuttgart. In U.S.A. and Canada, Intercontinental Medical Book Corporation, New York N. Y. 10016, 1968.

German-English: English-German Dictionary for Physicians. In two volumes. By Fritz Lejeune, Prof. Dr. med., Dr. phil., Dr. med. dent.; and Werner E. Bunjes, Lecturer in English, Germersheim Interpreters' College, Mainz University. Volume I. German-English. Cloth. Pp. 460. Price, DM 64.–. Georg Thieme Verlag, Stuttgart. In U.S.A. and Canada, Intercontinental Medical Book Corporation, New York, N.Y. 10016, 1968.

Equivalence of Medical Qualifications and the Practice of Medicine: A Survey of Existing Legislation. Offprint from Volume 18, No. 3 of the International Digest of Health Legislation. World Health Organization, Geneva. Paper. Pp. 47. Price, \$1.00. Columbia University Press, 136 South Broadway, Irvington-on-Hudson, N. Y. 10533, 1967.

SOCIETY PROCEEDINGS

MEETINGS OF RADIOLOGICAL SOCIETIES*

United States of America

American Roentgen Ray Society
Secretary, Dr. Ted F. Leigh, Emory University Clinic, Atlanta, Ga. 30322. Annual Meeting: Jung Hotel, New Orleans, La., Oct. 1–4, 1968.

American Radium Society
Secretary, Dr. Fernando G. Bloedorn, Department of Therapeutic Radiology, New England Medical Center Hospitals, 171 Harrison Ave., Boston, Mass. 02111. Annual meeting: Hotel Fontainebleau, Miami Beach, Fla., April 7-11, 1968.

Radiological Society of North America
Secretary-Treasurer, Dr. Maurice Doyle Frazer, 1744 South Fifty-eighth St., Lincoln, Neb. Annual meeting: Palmer House, Chicago, Ill., Dec. 1–6, 1968.

American College of Radiology
Executive Director, William C. Stronach, 20 N. Wacker Drive, Chicago 6, Ill. Annual meeting: Regency Hyatt House, Atlanta, Ga., Feb. 18–22, 1969.

Section on Radiology, American Medical Association
Secretary, Dr. Kenneth L. Krabbenhoft, Harper Hospital, Detroit, Mich. 48201. Annual meeting: San Francisco, Calif., June 16–20, 1968.

American Board of Radiology
Secretary, Dr. H. Dabney Kerr. Correspondence should be directed to Kahler Hotel Building, Rochester, Minn.

The Spring 1968 oral examination will be held at the Fontainebleau Hotel, Miami Beach, Florida, June 10–14, inclusive. The deadline for filing applications was December 31, 1967. Candidates eligible for this examination will not be required to take the written examination.

The first written examination will be held the latter half of June 1968 in various centers of the country for all residents having completed 3 years of approved training as of June 30, 1968. Deadline for filing for this examination and the oral examination of December 1968 was December 31, 1967.

American Association of Physicists in Medicine
Secretary, Leonard Stanton, Hahnemann Medical College, 230 N. Broad St., Philadelphia, Pa. 19102. Annual meeting to be announced.

American Society of Therapeutic Radiologists
Secretary, Dr. J. A. del Regato, Penrose Cancer Hospital, Colorado Springs, Colo. 80907.

American Society for Diagnostic Ultrasound
Secretary, Dr. Charles C. Grossman, 552 N. Neville St., Pittsburgh, Pa. 15213.

Twelfth International Congress of Radiology
President, Dr. Kempo Tsukamoto, 9-1, 4-chome, Angewa, Chiba, Japan. Meeting: Hotel New Otani, Tokyo, Japan, Oct. 6–11, 1969.

Tenth Inter-American Congress of Radiology
Counselor for the United States, Dr. Juan A. del Regato, Penrose Cancer Hospital, 2215 North Cascade Ave., Colorado Springs, Colo. 80907.
President, Dr. Juan A. del Regato, Colorado Springs, Colo., USA.
Secretary, Dr. F. Bloedoon, Boston, Mass., USA.
Meeting: San Juan, Puerto Rico, 1971.

Inter-American College of Radiology
President, Dr. Oscar Soto, H. Urteaga 480, Lima, Perú.

Alabama Radiological Society
Secretary, Dr. Walter Brower, Birmingham, Ala. Meets time and place of Alabama State Medical Association.

Alaska Radiological Society
Secretary, Dr. Bruce C. Wright, Providence Hospital, Anchorage, Alaska. Meets third Wednesday each month.

Arizona Radiological Society
Secretary-Treasurer, Dr. Robert E. Steyskal, 550 W. Thomas Rd., Phoenix, Ariz. 85013. Two regular meetings a year. Annual meeting at time and place of State Medical Association and interim meeting six months later.

Arkansas Chapter of American College of Radiology
Secretary-Treasurer, Dr. Neil E. Crow, Holt-Krock Clinic, 1500 Dodson Ave., Fort Smith, Ark. 72901.

Arkansas Radiological Society
Secretary, Dr. Charles W. Anderson, 1108½ Poplar, Pine Bluff, Ark. Meets every three months and also at time and place of State Medical Association.

Association of University Radiologists
Secretary-Treasurer, Dr. Harry Z. Mellins, S.U.N.Y. College of Medicine, Brooklyn, New York 11201. Annual Meeting: Ohio State University School of Medicine, Columbus, Ohio, May 9–11, 1968.

Atlanta Radiological Society
Secretary, Dr. Donald R. Rooney, Burnt Hickory Road, Marietta, Ga. Meets monthly except during three summer months, on third Tuesday, at the Academy of Medicine, Atlanta, Ga., at 8:00 P.M.

Bavarian-American Radiologic Society
Secretary, Colonel Kurt Harrell, Landstuhl Army Medical Center, Landstuhl, Germany. Meets quarterly.

Blockley Radiological Society
Secretary-Treasurer, Dr. R. John Gould, 41 Lombardy Rd., Drexel Hill, Pa. 19026.

Bluegrass Radiological Society
Secretary-Treasurer, Dr. Joe Bernard, Central Baptist Hosp., Lexington, Kentucky 40503. Meets quarterly.

Brooklyn Radiological Society
Secretary, Dr. Skottowe DePass, 69-13 Forest Ave., Brooklyn, N. Y. 11227. Meets first Thursday of each month, October through June.

Buffalo Radiological Society
Secretary, Dr. Richard Sheehan, 36 Briarlee Drive, Tonawanda, N. Y. Meets second Monday evening each month, October to May inclusive.

California Radiological Society
Secretary, Dr. James J. McCort, Santa Clara Valley Med. Ctr., San Jose, Calif. Meets annually during meeting of California Medical Association.

Catawba Valley Radiological Society
Secretary, Dr. Emmett R. White, P. O. Box 303, Rutherford College, N. C. 28671. Meets every Friday, Dept. of Radiology, Valdese General Hosp., Valdese, N. C., at 12:00 NOON.

Central New York Radiological Society
Secretary-Treasurer, Dr. Robert A. Bornhurst, State Univ. Hospital, 750 E. Adams St., Syracuse, N. Y. 13210. Meets first Monday each month, October through May.

Central Ohio Radiological Society
Secretary, Dr. Ollie E. Southard, 2787 Tudor Rd., Columbus, O. 43209. Meets second Thursday in October, November, January, and March 15 and May 19 at Fort Hayes Hotel, Columbus, Ohio.

Chicago Roentgen Society
Secretary-Treasurer, Dr. Fredric D. Lake, 2548 N. Lakeview Ave., Chicago, Ill. 60614. Meets second Thursday of each month, October to April, except December, at the Pick-Congress Hotel at 8:00 P.M.

Cleveland Radiological Society
Secretary-Treasurer, Dr. Theodore J. Castele, 18869 Canyon Rd. Parkview Park, Ohio 44126. Meetings at 7:00 P.M. on fourth Monday of October, November, January, February, March and April.

*** Secretaries of societies are requested to send timely information promptly to the Editor.**

[illegible] Radiological Society
[illegible] Charles E. Seibert, Denver Gen. Hosp., [illegible] 80218. Meets third Friday of each month [illegible] Athletic Club from September through May.

[illegible] Valley Radiologic Society
[illegible], Dr. William W. Walthall, Jr., 130 Maple St., [illegible]field, Mass. Meets in April and October.

[illegible] Fort Worth Radiological Society
[illegible] Treasurer, Dr. Robert J. Atcheson, 1401 S. [illegible] Fort Worth, Texas 76104. Meets monthly, [illegible] Monday, at Southwest International Airport at 6:30 P.M.

Detroit Roentgen Ray and Radium Society
Secretary, Dr. Robert L. Willis, Harper Hospital, Detroit, Mich. 48201. Meets monthly, first Thursday, October through May, at David Whitney House, 1010 Antietam, at 6:30 P.M.

East Bay Radiological Society
Secretary, Dr. Tom H. Piatt, 12 Camino Encinas, Orinda, Calif. 94563. Meets first Thursday each month, Oct. through May, at University Club, Oakland, Calif.

East Tennessee Radiological Society
Secretary-Treasurer, Dr. T. F. Haase, Jr., 205 Medical Arts Building, Knoxville, Tenn. Meets in January and September.

Florida Radiological Society
Secretary, Dr. John C. Jowett, Orlando, Fla. Meets twice annually, in the spring with the annual State Society Meeting and in the fall.

Florida West Coast Radiological Society
Secretary-Treasurer, Allen M. Sheer, 501 E. Buffalo Ave., Tampa, Fla. 33603. Meets in January, March, May, July, September and November.

Georgia Radiological Society
Secretary, Dr. J. L. Clements, Jr., 134 LaGrange St., Newman, Georgia 30263. Meets in spring and fall with Annual State Society Meeting.

Greater Cincinnati Radiological Society
Secretary-Treasurer, Dr. Owen L. Brown, 2421 Auburn Ave., Cincinnati, Ohio 45219.

Greater Louisville Radiological Society
Secretary-Treasurer, Dr. L. D. LeNeave, 315 E. Broadway, Louisville, Ky. 40202. Meets monthly.

Greater Miami Radiological Society
Secretary-Treasurer, Dr. Sylvan H. Sarasohn, North Miami General Hospital, 1701 Northeast 127th St., North Miami, Fla. 33161. Meets monthly, third Wednesday at 8:00 P.M. at Jackson Memorial Hospital, Miami, Fla.

Greater St. Louis Society of Radiologists
Secretary-Treasurer, Dr. Alexander J. Link, 7215 Maryland, St. Louis, Mo. 63130.

Hawaii Radiological Society
Secretary-Treasurer, Dr. R. K. Wang, P.O. Box 256, Wahiawa, Oahu 96786. Meets third Monday of each month at 7:30 P.M.

Health Physics Society
Secretary, John W. Thomas, Philadelphia, Pa. Annual Meeting: Denver-Hilton Hotel, Denver, Colo., June 16–20, 1968.

Houston Radiological Society
Secretary, Dr. Thomas S. Harle, 1200 Moursond Drive, Houston, Tex. 77025. Meets fourth Monday of each month, except June, July, August and December, at the Doctors' Club, 8:00 P.M., Houston, Tex.

Idaho State Radiological Society
Secretary, Dr. George H. Harris, Bannock Memorial Hospital, Pocatello, Idaho. Meets in the spring and fall.

Illinois Radiological Society
Secretary, Dr. George A. Miller, Carle Hospital Clinic, Urbana, Ill. Meets in the spring and fall.

Indiana Roentgen Society, Inc.
Secretary, Dr. Edwin F. Koch, Jr., 915 University Ave., Muncie, Ind. 47303. Meets first Sunday in May and during fall meeting of Indiana State Medical Association.

Iowa Radiological Society
Secretary, Dr. L. L. Maher, 1419 Woodland Ave., Des Moines, Iowa. Luncheon and business meeting during annual session of Iowa State Medical Society. The scientific section is held in the autumn.

Kansas Radiological Society
Secretary-Treasurer, Dr. Robert C. Lawson, 310 Medical Arts Bldg., 10th and Horne, Topeka, Kan. Meets in spring with State Medical Society and in winter on call.

Kentucky Chapter, American College of Radiology
Secretary-Treasurer, Dr. Ralph C. Quillin, 1221 S. Broadway, Lexington, Ky. 40504. Meets in April and September.

Kings County Radiological Society
Secretary, Dr. Sidney Hendler, 1880 Ocean Ave., Brooklyn 30, N. Y. Meets Kings County Med. Soc. Bldg. monthly on fourth Thursday, October to May, 8:45 P.M.

Knoxville Radiological Society
Secretary, Dr. Clifford L. Walton, Blount Professional Bldg., Knoxville 20, Tenn. Meetings are held the third Monday of every other month at the University of Tennessee Memorial Research Center and Hospital.

Long Island Radiological Society
Secretary, Dr. Robert J. Hochstim, 1200 Stewart Ave., Garden City, N. Y. 11533. Meets monthly.

Los Angeles Radiological Society
Secretary, Dr. Harvey I. Meyers, 2010 Wilshire Blvd., Los Angeles, Calif. 90057. Meets second Wednesday of month in September, November, January, April and June at Los Angeles County Medical Association Building, Los Angeles, Calif.

Louisiana-Texas Gulf Coast Radiological Society
Secretary-Treasurer, Dr. Edward A. Sheldon, 109 Doctors Bldg., Beaumont, Texas 77701.

Maine Radiological Society
Secretary-Treasurer, Dr. Robert A. Bearor, Maine Medical Center, Portland, Maine 04102. Meets in June, September, December and April.

Maryland Radiological Society
Secretary, Dr. Henry Startzman, Medical Arts Building, Baltimore, Md.

Memphis Roentgen Society
Secretary-Treasurer, Dr. Vernon I. Smith, Jr., Suite 203, 1085 Madison Ave., Memphis, Tenn. 38104. Meets first Monday of each month at John Gaston Hospital.

Miami Valley Radiological Society
Secretary, Dr. Darwood B. Hance, Reid Memorial Hospital, Richmond, Indiana. Meets third Thursday of fall, winter and spring months at 7:30 P.M. at Miami Valley Hospital, Dayton, Ohio.

Mid-Hudson Radiological Society
Secretary-Treasurer, Dr. Herbert S. Berlin, Hopewell Junction, N. Y. Meets 7:00 P.M., first Wednesday of each month, September to May.

Milwaukee Roentgen Ray Society
Secretary-Treasurer, Dr. James E. Bell, 8700 W. Wisconsin Ave., Milwaukee, Wis. 53213. Meets monthly on fourth Monday, October through May, at University Club.

Minnesota Radiological Society
Secretary-Treasurer, Dr. Edward A. Peterson, 572 Lowry Medical Arts Bldg., St. Paul, Minn. Meets twice annually, fall and winter.

Mississippi Radiological Society
Secretary-Treasurer, Dr. Dan T. Keel, Jr., 504 Chippewa St., Brookhaven, Miss. Meets third Thursday of each month at the Heidelberg Hotel, Jackson, at 6:00 P.M.

Missouri Radiological Society
Secretary-Treasurer, Dr. Harold B. Rapp, Cape Girardeau, Mo.

Montana Radiological Society
Secretary, Dr. Clark Grimm, Great Falls, Montana. Meets at least once a year.

Nebraska State Radiological Society
Secretary-Treasurer, Dr. Otto A. Troester, 924 Sharp Building, Lincoln, Nebraska 68508. Meets third Wednesday of each month at 6 P.M. in Omaha or Lincoln.

Nevada Radiological Society
Secretary, Dr. William G. Arbonies, Department of Radiology, St. Mary's Hospital, Reno, Nev.

New England Roentgen Ray Society
Secretary, Dr. Morris Simon, 330 Brookline Ave., Boston, Mass. 02153. Meets third Friday of each month, October through May, at The Longwood Towers, 20 Chapel Street, Brookline, Mass., at 4:30 P.M.

New Hampshire Roentgen Ray Society
Secretary, Dr. Paul Y. Hasserjian, 1470 Elm St., Manchester, N. H. Meets four to six times yearly.

New Mexico Association of Radiologists
Secretary-Treasurer, Dr. Justin J. Wolfson, Department of Radiology, Bernalillo County-Indian Hospital, Albuquerque, New Mexico.

New Mexico Society of Radiologists
Secretary, Dr. Phil Fox, Albuquerque, New Mexico. Four meetings annually, three held in Albuquerque, N. M., and one held at time and place of New Mexico State Medical Society annual meeting.

New York Roentgen Society
Secretary, Dr. David H. Baker, Babies Hospital, 3975 Broadway, New York, N. Y. 10032. Meets monthly on third Monday at the New York Academy of Medicine at 4:30 P.M. Annual meeting: April 25–28, 1968.

North Carolina Chapter of ACR.
Secretary-Treasurer, Dr. Ira Bell, Hickory, N. C. Annual meeting to be announced.

North Carolina Radiological Society
Secretary, Dr. E. H. Schultz, North Carolina Memorial Hospital, Chapel Hill, N. C. Meets in the spring and fall each year.

North Dakota Radiological Society
Secretary, Dr. A. Ohrt, 408 Medical Arts Bldg., Fargo, N. D. 58102. Meets at time of State Medical Association meeting. Other meetings arranged on call of the President.

North Florida Radiological Society
Secretary, Dr. Charles H. Newell, 800 Miami Road, Jacksonville 7, Fla. Meets quarterly in March, June, September and December.

Northeastern New York Radiological Society
Secretary, Dr. Anthony J. Tabacco, 621 Central Ave., Albany 6, N. Y. Meets in Albany area on second Wednesday of October, November, March and April.

Northern California Radiological Society
Secretary-Treasurer, Ivan D. Siddons, 3701 J. St., Suite 106, Sacramento, Calif. 95816. Meets fourth Monday of Sept., Nov., Jan., March and May at the Sutter Club in Sacramento.

Northwestern Ohio Radiological Society
Secretary, Dr. Vito J. Zupa, Mercy Hospital, Department of Radiology, Toledo, Ohio.

Ohio State Radiological Society
Secretary, Dr. Robert D. Berkebile Elyria Memorial Hospital, Elyria, Ohio 44035.

Oklahoma State Radiological Society
Secretary, Dr. Donald F. Mauritson, 100 Utica Square Med. Center, Tulsa, Okla. 74114. Meets in January, May and October.

Orange County Radiological Society
Secretary, Dr. George W. Logan, 301 Newport Blvd., Newport Beach, Calif. Meets fourth Tuesday of every month at Orange County Medical Association Building.

Oregon Radiological Society
Secretary-Treasurer, Dr. Irving J. Horowitz, 2311 N.W. Northrup Str., Portland, Ore. 97210. Meets on second Wednesday of month, October through April, at the University Club, Portland, Ore.

Orleans Parish Radiological Society
Secretary, Dr. Joseph V. Schlosser, Charity Hospital, New Orleans 13, La. Meets second Tuesday of each month.

Pacific Northwest Radiological Society
Secretary-Treasurer, Dr. Marvin Wallace, 555 108th Ave. N. E., Bellevue, Washington 98004. The 22nd Annual Meeting will be held at the Olympic Hotel, Seattle, Washington, May 3–5, 1968.

Pennsylvania Radiological Society
Secretary, Dr. T. Frederick Weiland, 619 Ridgeway Ave., Grove City, Pa. 16127. Annual meeting to be announced.

Philadelphia Roentgen Ray Society
Secretary, Dr. C. Jules Rominger, Misericordia Hospital, 54th St. and Cedar Ave., Philadelphia, Pa. 19143. Meets first Thursday of each month at 5 P.M., from October to May in Thompson Hall, College of Physicians.

Pittsburgh Roentgen Society
Secretary, Dr. Edward R. Seitz, 601 Jenkins Bldg., Pittsburgh, Pa. 15222. Meets second Wednesday of month, October through June, at Park Schenley Restaurant.

Radiological Society of Connecticut, Inc.
Secretary-Treasurer. Dr. Henry J. Fox, 10 Washington Ave., Bridgeport, Conn. Meetings are held quarterly.

Radiological Society of Greater Cinci[illegible]
Secretary-Treasurer, Dr. Donald E. Gu[illegible] Bayard Dr., Cincinnati, Ohio 45208. Meets [illegible] of each month at Cincinnati Academy of Medic[illegible]

Radiological Society of Greater Kansas City
Secretary, Dr. J. Stewart Whitmore, 1010 Rial[illegible] Kansas City, Mo. Meets last Friday of each m[illegible]

Radiological Society of Kansas City
Secretary, Dr. Arthur B. Smith, 800 Argyle Bld[illegible] City, Mo. Meets third Thursday of each mon[illegible]

Radiological Society of Louisiana
Secretary, Dr. Lester W. Eavenson, 2700 Na[illegible]on Ave, New Orleans 15, La. Meets semiannually, during Louisiana State Medical Society meeting and 6 months later.

Radiological Society of New Jersey
Secretary, Dr. John W. Marquis, 12 Hawthorne Ave., East Orange, N. J. 07018. Meets in Atlantic City at time of State Medical Society meeting and in October or November in Newark, N. J.

Radiological Society of Rhode Island
Secretary-Treasurer, Dr. John M. Vesey, 1196 Elmwood Ave., Cranston, R. I.

Radiological Society of South Dakota
Secretary-Treasurer, Dr. Donald J. Peik, 303 S. Minnesota Ave., Sioux Falls, S. D.

Radiological Society of Southern California
Secretary-Treasurer, Dr. Robert G. Williams, The Santa Barbara Medical Clinic, P.O. Box 1200, Santa Barbara, Calif. 93102. Meets three times a year, usually October, February and May.

Radiological Society of the State of New York
Secretary-Treasurer, Dr. John W. Colgan, 273 Hollywood Ave., Rochester 18, N. Y.

Redwood Empire Radiological Society
Secretary, Dr. Lee F. Titus, 164 W. Napa St., Sonoma, Calif. Meets second Monday every other month.

Richmond County Radiological Society
Secretary, Dr. W. F. Hamilton, Jr., University Hospital, Augusta, Ga. Meets first Thursday of each month at various hospitals.

Rochester Roentgen Ray Society, Rochester, N. Y.
Secretary, Dr. Kenneth E. Robinson, Rochester General Hospital, 1425 Portland Ave., Rochester, N. Y. 14621. Meets at 8:15 P.M. on the last Monday of each month, September through May, at Strong Memorial Hospital.

Rocky Mountain Radiological Society
Secretary-Treasurer, Dr. Robert W. Lackey, 4200 E. Ninth Ave., Denver, Colo. Annual meeting: Brown Palace Hotel, Denver, Colo., Aug. 15–17, 1968.

San Antonio-Military Radiological Society
Secretary, Dr. Hugho F. Elmendorf, Jr., 730 Medical Arts Bldg., San Antonio 5, Tex. Meets third Wednesday of each month in Fort Sam Houston Officer's Club at 6:30 P.M.

San Diego Radiological Society
President-Secretary, Charles R. Henkelmann, 3909 Palm Drive, Bonita, Calif. 92002. Meets first Wednesday of each month at the Town & Country Motel.

San Francisco Radiological Society
Secretary, Dr. H. Joachim Burhenne, Children's Hospital and Adult Medical Center, 3700 California St., San Francisco, Calif. 94119. Meets quarterly at the San Francisco Medical Society, 250 Masonic Ave., San Francisco, Calif. 94118.

Santa Clara County Radiological Society
Secretary, Dr. D. Brendan O'Donnell, 696 E. Santa Clara St., San Jose, Calif. 95112. Meets monthly at the Santa Clara County Medical Association Bldg., 700 Empey Way, San Jose, Calif.

Section on Radiology, California Medical Association
Secretary, Dr. William H. Graham, 630 East Santa Clara St., San Jose, Calif.

Section on Radiology, Medical Society of the District of Columbia
Secretary-Treasurer, Dr. Louis Wener, Cafritz Memorial Hosp., 1310 Southern Ave., S.E., Washington, D. C. 20032. Meets at Medical Society Library, third Wednesday of January, March, May and October at 8:00 P.M.

Section on Radiology, Southern Medical Association
Secretary, Dr. Andrew F. Giesen, Jr., White-Wilson Clinic, Fort Walton Beach, Fla. 32548. Annual meeting to be announced.

[illegible]tion on Ra[illegible]ology, Texas Medical Association
[illegible]ecretary, D[illegible] [illegible]eorge F. Crawford, St. Elizabeth Hospi[illegible], Beaumont, Tex. Meets annually with the Texas [illegible] [illegible]ssociation.

S[illegible]port Radiological Club
[illegible]ary, Dr. W. R. Harwell, 608 Travis St., Shreveport, [illegible] [illegible]ts monthly on third Wednesday at 7:30 P.M., [illegible]ber to May inclusive.

Soc[illegible] for Pediatric Radiology
[illegible] Dr. John L. Gwinn, Children's Hospital, 4614 Sunset Blvd., Los Angeles 27, Calif. Annual meeting: Jung [illegible], New Orleans, La., Sept. 30, 1968.

Society of Nuclear Medicine
Secretary, Mr. C. Craig Harris, Oak Ridge National Laboratories, Oak Ridge, Tenn. *Administrator*, Mr. Samuel N. Turiel, 430 N. Michigan Ave., Chicago 11, Ill. Annual meeting Chase-Park Plaza Hotel, St. Louis, Mo., June 27–30 1968.

South Bay Radiological Society
Secretary, Dr. Emerson C. Curtis, University Dr., Menlo Park, Calif. 94025. Meets second Wednesday of each month.

South Carolina Radiological Society
Secretary, Dr. George W. Brunson, 1406 Gregg St., Columbia, S. C. Annual meeting (primarily business) in conjunction with the South Carolina Medical Association meeting in May. Annual fall scientific meeting at time and place designated by the president.

South Dakota Radiological Society
Secretary, Dr. Donald J. Peik, 1417 S. Minnesota Ave., Sioux Falls, S. Dak. Meets in spring with State Medical Society and in fall.

Southern California Radiation Therapy Society
Secretary-Treasurer, Dr. Aaron G. Fingerhut, 1000 W. Carson St., Torrance, Calif. 90502. Mets quarterely.

Southern Radiological Conference
Secretary-Treasurer, Dr. Marshall Eskridge, Mobile Infirmary, P.O. Box 4097, Mobile, Ala. 36604. Annual meeting: Grand Hotel, Pointe Clear, Ala. 36564, Jan. 31–Feb. 2, 1969.

Southwestern Radiological Society
Secretary, John M. McGuire, 904 Chelsea, El Paso, Tex. Meets last Monday of each month at 6:30 P.M. in the Paso del Norte Hotel.

Tennessee Radiological Society
Secretary-Treasurer, Dr. Marion E. Spurgeon, Memorial Hosp., Clarksville, Tenn. Meets annually at the time and place of the Tennessee State Medical Association meeting.

Texas Radiological Society
Secretary, Dr. Herman C. Sehested, 815 Medical Arts Bldg., Fort Worth 2, Tex. Annual meeting to be announced.

Tri-State Radiological Society
Secretary, Dr. John H. Marchand, Jr., Methodist Hospital, Henderson, Ky. Meets third Wednesday of Oct., Jan., March and May, 8:00 P.M., Elks Club in Evansville, Ind.

University of Michigan Department of Roentgenology Staff Meeting
Meets each Monday evening from September to June, at 7:00 P.M. at University Hospital, Ann Arbor Mich.

[illegible]Peninsula Radiological Society
Secretary, Dr. A. Gonty, Menominee, Mich. Meets quarterly.

Utah State Radiological Society
Secretary-Treasurer, Dr. Leon M. Neal, St. Benedict's Hospital, 3000 Polk Ave., Ogden, Utah 84403. Meets fourth Wednesday in January, March, May, September and November at Holy Cross Hospital.

Vermont Radiological Society
Secretary, Dr. John R. Williams, 160 Allen St., Rutland, Vt.

Virginia Radiological Society
Secretary-Treasurer, Dr. K. Kenneth Wallace Jr., Norfolk, Va.

Washington State Radiological Society
Secretary, Dr. Owen Marten, 930 Terry Avenue, Seattle, Wash. Meets quarterly.

West Virginia Radiological Society
S[illegible]cretary, D[illegible] George G. Green, Morgantown, W. Va. [illegible]ts concurrently with Annual Meeting of West Virginia State Medical Society; other meetings arranged by program committee.

Westchester County Radiological Society
Secretary, Dr. Arnold Gerson, Medical Arts Bldg., Mt. Vernon, N. Y. Meets on third Tuesday of January and October and on two other dates.

Wisconsin Radiological Society
Secretary-Treasurer, Harold F. Ibach, 2400 W. Villard Ave., Milwaukee, Wis. 53209. Meets twice a year, May and September.

Wyoming Radiological Society
Secretary, Dr. J. D. Grant, Memorial Hosp., Sheridan, Wyo. Meets in fall with State Medical Society and in spring on call of President.

Cuba, Mexico, Puerto Rico and Central America

Asociación de Radiólogos de Centro America y Panamá. Comprising: Guatemala, El Salvador, Honduras, Nicaragua, Costa Rica and Panamá.
Secretary-General, Dr. Roberto Calderón, Calle Central Oeste No. 218, Managua, Nicaragua, Central America. Meets annually in a rotating manner in the six countries.

Sociedad de Radiología de El Salvador
Secretary, Dr. Julio Astacio, 5a Av. Nte. No. 434, San Salvador, Rep. El Salvador.

Sociedad de Radiología de Guatemala
Secretary, Dr. Carlos E. Escobar, 9ª. Calle A 0-05, Zona 1, Guatemala.

Sociedad de Radiología y Fisioterapía Cubana
Secretary, Dr. Miguel A. García Plasencia, Hospital Curie, 29 y F, Vedado, Habana, Cuba Meets monthly at Curie Hospital.

Sociedad Costarricense de Radiologia
Secretary, Dr. James Fernández Carballo, Apartado VIII, San José, Costa Rica.

Sociedad Mexicana de Radiología, A.C.
Coahuila No. 35, México 7, D. F.
Secretary-General, Dr. Ramón Ruenes.
Meets first Monday of each month.

Asociación Puertorriqueña de Radiología
Secretary, Dr. R. B. Díaz Bonnet, Suite 504. Professional Bldg., Santurce, Puerto Rico.

Sociedad Radiológica Panameña
Secretary, Dr. L. Arrieta Sánchez, Apartado No. 6323, Panamá, R. de P. Meets monthly in a department of radiology of a local hospital chosen at preceding meeting.

Sociedad Radiológica de Puerto Rico
Secretary, Dr. Felipe N. de Jesús, Apt. 9387, Santurce, Puerto Rico. Meets second Thursday of each month at 8:00 P.M. at the Puerto Rico Medical Association Bldg. in San Juan.

British Commonwealth of Nations

Association of Radiologists of the Province of Quebec
Secretary, Dr. R. Robillard, Notre-Dame Hospital, 1560 Sherbrooke St., East, Montreal, Que., Canada. Meets four times a year.

British Institute of Radiology
Honorary Secretary, Dr. G. H. du Boulay, 32 Welbeck St., London, W. 1, England. Meets monthly from October until May. Annual meeting to be announced.

Canadian Association of Physicists, Division of Medical and Biological Physics.
Honorary Secretary-Treasurer, Paul M. Pfalzner, Dept. of Therapeutic Radiology, University of Western Ontario, London, Ont., Canada. Annual meeting to be announced.

Edmonton and District Radiological Society
Secretary, J. D. R. Miller, M.B., University of Alberta Hospital, Edmonton, Alberta, Canada. Meets third Thursday of each month October to May, except December, at various Edmonton Hospitals.

Faculty of Radiologists
Honorary Secretary, Dr. J. N. Pattinson, 47 Lincoln's Inn Fields, London, W.C.2, England. Annual meeting: London, England, June 21–22, 1968.

Faculty of Radiologists, Royal College of Surgeons in Ireland
Registrar, Dr. H. O'Flanagan, F.R.C.P.I., D.P.H., 123 St. Stephens Green, Dublin 2, Ireland.

Section of Radiology of the Royal Society of Medicine (Confined to Medical Members)
Meets third Friday each month at 4:45 P.M. at the Royal

Society of Medicine, 1 Wimpole St., London, W. 1, England.

Canadian Association of Radiologists

Honorary Secretary-Treasurer, Dr. Maurice Dufresne, *Associate Honorary Secretary-Treasurer*, Dr. F. Robert MacDonald, 1555 Summerhill Ave., Montreal 25, Que., Canada. Thirty-first Annual Meeting, Chateau Frontenac, Quebec, March 4–9, 1968.

Montreal Radiological Study Club

Secretary, Dr. Leonard Rosenthall, Montreal General Hospital, Montreal, Que., Canada. Meets first Tuesday evening, October to April.

Section of Radiology, Canadian Medical Association

Secretary, Dr. C. M. Jones, Inglis St., Ext. Halifax, N. S.

Société Canadienne-Française de Radiologie

Secretary General, Dr. Jacques Lespérance, 5415 Boul. L'Assomption, Montreal 26, P. Q., Canada. Meets every third Tuesday from October to April. Annual meeting to be announced.

Toronto Radiological Society

Secretary, Dr. George Wortzman, Toronto General Hosp., Toronto 12, Ont., Canada. Meets second Monday of each month, September through May.

College of Radiologists of Australasia

Honorary Secretary, Dr. T. P. Loneragan, c/o British Medical Agency, 135 Macquarie St., Sydney, N.S.W., Australia.

South America

Asociación Argentina de Radiología

Secretary, Dr. Lidio G. Mosca, Avda. Gral. Paz 151, Córdoba, Argentina. Meetings held monthly.

Ateneo de Radiologia

Secretary, Dr. Victor A. Añaños, Instituto de Radiologia, Santa Fe 3100, Rosario, Argentina. Meets monthly on second and fourth Fridays at 7:00 P.M. in the Hospital Nacional de Centenario, Santa Fe 1300, Rosario.

Colégio Brasileiro de Radiologia

Secretary-General, Dr. Miguel Mario Céntola, Caixa Postal 5984, São Paulo, Brazil.

Sociedad Argentina de Radiologia

Secretary-General, Dr. Osvaldo E. Zerbo, Santa Fe 1171, Buenos Aires. Meetings are held monthly.

Sociedad Boliviana de Radiología

Secretary, Dr. Javier Prada Méndez, Casilla 1182, La Paz, Bolivia. Meets monthly. General assembly once every two years.

Sociedade Brasileira de Radiologia

Secretary, Dr. Armando Rocha Amoédo, Cxa Postal 1532, Rio de Janeiro, Brazil. General Assembly meets every two years in December.

Sociedade Brasileira de Radioterapia

Secretary, Dr. Oscar Rocha von Pfuhl, Av. Brigadeiro Luiz Antonio, 644, São Paulo, Brazil. Meets monthly on second Wednesday at 9:00 P.M. in São Paulo at Av. Brigadeiro Luiz Antonio, 644.

Sociedad Chilena de Radiología

Secretary, Dr. Manuel Concha, Casilla 13426, Santiago, Chile. Meets fourth Friday of each month.

Sociedad Colombiana de Radiologia

Secretary-General, Dr. Armando Uribe, Hospital Militar Central, Apartado aéreo No. 5804, Bogotá, Colombia. Meets last Thursday of each month.

Sociedad Ecuatoriana de Radiología y Fisioterapía

Secretary, Dr. Carlos Palau, Av. Bogotá 206, Guayaquil, Ecuador.

Sociedad Paraguaya de Radiología

Secretary, Dr. Miguel González Addone, 15 de Agosto 322, Asunción, Paraguay.

Sociedad Peruana de Radiologia

Secretary-General, Dra. Ladys del Pino, Instituto de Radiología "Cayetano Heredia" Hospital Arzobispo Loayza, Lima, Perú. Meets monthly except during January, February and March.

Sociedad de Radiologica del Atlantico

Secretary, Dr. Raul Fernandez, Calle 40 #41-110, Baranquilla, Colombia. Society meets monthly at the Instituto de Radiología.

Sociedad de Radiología, Cancerología y Física Médica del Uruguay

Secretary-General, Dr. Ernesto H. Cibils, Av. Agraciada 1464, piso 13, Montevideo, Uruguay.

Sociedade de Radiología de Pernambuco

Secretary, Dr. Manoel Medeiros, Instituto de Radiologia da Faculdade de Medicina da Universidade do Recife, Caixa Postal 505, Pernambuco, Brazil.

Sociedad de Roentgenología y Medicina Nuclear de la Provincia de Córdoba

Secretary-General, Dr. Lucas C. Di Rienzo, Ave. Gral. Paz. 151, Córdoba, Argentina.

Sociedad Venezolana de Radiología

Secretary-General, Dr. Modesto Rivero González, Apartado No. 9362 Candelaria, Caracas, Venezuela. Meets monthly, third Friday at Colegio Médico del Distrito Federal, Caracas.

Continental Europe

Österreichische Röntgen-Gesellschaft

President, Dr. Konrad Weiss, Mariannengasse 10, Vienna 9, Austria. Meets second Tuesday of each month in Allgemeine Poliklinik. Annual meeting to be announced.

Société Belge de Radiologie

General Secretary, Prof. Simon Masy, Louvain, Belgium. Meets in February, March, May, June, September, October, November and December.

Société Européenne de Radiologie Pédiatrique

Permanent Secretary, Dr. Jaques Sauvegrain, Hôpital des Enfants-Malades, 149, rue de Sèvres, Paris 15e, France. *General Secretary*, Dr. H. Ludin, Department of Roentgenology, Basler Kinderspital, Basel, Switzerland. Annual meeting to be announced.

Société Française d'Electroradiologie Médicale, and its branches: Société du Sud-Ouest, du Littoral Méditerranéen, du Centre et du Lyonnais, du Nord, de l'Ouest, de l'Est, et d'Alger et d'Afrique du Nord. Central Society meets third Monday of each month, except during July, August and September, rue de Seine 12, Paris, France.

Secretary-General, Dr. Ch. Proux, 9 rue Daru Paris 8e, France.

Československá Společnost pro Roentgenologii a Radiologii

Secretary, Dr. Robert Poch, Praha 12, Srobárova 50, Czechoslovakia. Meets monthly except during July, August and September. Annual general meeting.

Deutsche Röntgengesellschaft

Secretary, Professor Dr. med. H. Lossen, Universitäts-Röntgeninstitut, Lagenbeckstr. 1, Mainz, Germany.

Società Italiana di Radiologia Medica e di Medicina Nucleare

Secretary, Dr. Ettore Conte, Ospedale Mauriziano, Torino, Italy. Meets annually.

Nederlandse Vereniging voor Radiologie

Secretary, Dr. C. B. A. J. Puijlaert, Prof. Dondersstraat 73, Tilburg, Netherlands.

Scandinavian Radiological Society

Secretary-General, Dr. C. E. Unnérus, Professor, Hagalund-Tapiola, Havsvindsvägen 5 C., Finland. Annual meeting: Copenhagen, Denmark, May 29–June 1, 1968.

Sociedad Española de Radiología y Electrología Médicas y Medicina Nuclear

Secretary, Juan Gomez Lopez, Villanueva, 11, Madrid 1. Meets every second Friday of each month, Oct. to June, inclusive, in Madrid. Annual general meeting to be announced.

Schweizerische Gesellschaft für Radiologie und Nuklearmedizin (Société Suisse de Radiologie et de Médecine Nucléaire)

Secretary, Dr. Max Hopf, Effingerstrasse 47, Bern, Switzerland.

Asia

Indian Radiological Association

Secretary, Dr. R. F. Sethna, Navsari Building, Hornby Road, Bombay 1, India.

Indonesian Radiological Society

Secretary, Professor Sjahriar Rasad, Taman Tjut Mutiah I Diakarta, Indonesia

Iranian Radiological Society

Secretary, Dr. Issa Yaghmai, P.O. Box No. 14-1151, Teheran, Iran. The Society meets on the second Saturday of each month.

ABSTRACTS OF RADIOLOGICAL LITERATURE

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ROENTGEN DIAGNOSIS

HEAD

GOODING, CHARLES A., CARTER, ANTHONY, and HOARE, RICHARD D. New ventriculographic aspects of the Arnold-Chiari malformation. *Radiology*, Oct., 1967, *89*, 626–632. (Address: C. A. Gooding, M.D., Letterman General Hospital, Presidio, San Francisco, Calif. 94129.)

The presence of caudal herniation of the cerebellum, brain stem, and fourth ventricle in the Arnold-Chiari malformation is well known. Not well known are the intracranial abnormalities described by Cameron in 1957 which consist of thickening of the interthalamic ramus (massa intermedia), hypoplasia of the falx cerebri, and partial obliteration of the great cerebral fissure. The authors report the results of a ventriculographic assessment of these pathologic aspects and others not commented upon and have come to recognize a unique appearance of the ventriculograms in Arnold-Chiari cases.

Ventriculograms of 62 patients with the Arnold-Chiari malformation, 50 patients with normal air studies, and 19 patients with aqueduct stenosis were analyzed. An abnormal anterior wall of the third ventricle was found in 40 (64 per cent) of the Arnold-Chiari cases, in none of the normal air studies, and only in 1 of the aqueduct stenosis cases. This irregularity was quite variable, but usually presented as a definite structure crossing the antero-inferior portion of the third ventricle, in a coronal plane. Occasionally this created the impression of a diverticulum-like outpouching through the anterior wall of the third ventricle. In all instances, its origin was definitely inferior to the anterior commissure and superior to the chiasmatic recess.

The massa intermedia was identifiable in 52 of the 62 patients with an Arnold-Chiari diagnosis (84 per cent), in 23 of the 50 patients in the normal group (46 per cent), and in 12 of the 19 patients with aqueduct stenosis (66 per cent). It was greater than 12 mm. in diameter in 9 of the Arnold-Chiari series, a finding not present in any of the other cases. Absence of the septum pellucidum resulting in fused lateral ventricles was found in 20 per cent of the Arnold-Chiari cases and in 21 per cent of the patients with aqueduct stenosis, and in only 1 of the normal series.

The inferior margins of the lateral ventricles, at the foramen of Monro, as seen in the brow-up antero-posterior view, were sharply pointed and medially directed in 32 of the 62 Arnold-Chiari patients (51 per cent), in 1 of the 50 normal cases (2 per cent), and in 2 of the 19 cases of aqueduct stenosis (10 per cent).

The deformity of the anterior portion of the third ventricle, whether secondary to enlarged commissural fibers crossing coronally or representing a ballooned third ventricle over the anterior communicating artery, is fairly specific for the Arnold-Chiari cases. A demonstrable massa intermedia in itself is of little consequence, but the exceptionally large massa intermedia was found solely in the Arnold-Chiari series, and was frequently seen in an inordinately anterior location.

No prognostic significance of the ventricular findings was evident as it was found that those Arnold-Chiari patients dying in childhood manifested these changes in the same proportion as those surviving. It is the authors' belief that these pneumographic entities when considered as a complex, may be as pathognomonic of the Arnold-Chiari malformation as the demonstration of the caudal herniation of brain stem and cerebellum through the foramen magnum. This is of particular importance in cases of myelomeningocele with hydrocephalus in which the fourth ventricle cannot be demonstrated at ventriculography because of an associated stenosis of the aqueduct.—*Donald N. Dysart, M.D.*

GRANONE, F. G., and GRANONE, G. La pneumosubmaxillotomografia. (Pneumosubmaxillotomography.) *Radiol. med.*, 1967, *53*, 737–748. (From: Istituto di Radiologia dell'Università di Torino, Torino, Italy.)

Described is a technique for the visualization of the submandibular region by the introduction of CO_2 associated with tomography.

The patient is placed supine with the head extended. A 22 gauge needle is introduced 1.5–2 cm. in front of the anterior insertion of the masseter and 1.5–2 cm. below the inferior margin of the mandible. At the same time that the needle is introduced a few cc. of procaine is injected. When it is felt that the needle has penetrated through the superficial cervical fascia, 70 to 80 cc. of CO_2 is introduced and about 10 minutes later tomographic studies of the submandibular region are performed in the 2 sagittal planes.

The authors have found this technique useful in patients in whom sialography through the duct of Wharton could not be performed or in those in whom an allergy to the usual contrast media was present.—*A. F. Govoni, M.D.*

NECK AND CHEST

CHÉRIGIÉ, E., TAVERNIER, C., DEPORTE, A., DOYON, D., CASTEL, A., and TAIEB, A. (Paris, France.) Radiologie cinétique de la région oeso-cardiotubérositaire. (Kinetic radiology of the esophago-cardio-tuberosity region.) *J. de radiol., d'électrol. et de méd. nucléaire*, Oct., 1967, *48*, 513–525.

In studying the lower third of the esophagus, cardia and tuberosity of the stomach the authors have developed a systematic approach, although no new modalities are employed. They routinely follow these 10 steps:

1. Progressive physiologic insufflation is achieved, and this is accomplished by having the patient swallow small gulps of barium, at the same time spluttering as if the mixture were too hot. This double contrast is especially useful in viewing the cardia, and is more effective than when medications are used. If the patient is unable to achieve this the more conventional method is followed, as it may be in some of the succeeding steps.
2. The pinching effect of the diaphragm is studied.
3. The active emptying of the phrenic ampoula is followed.
4. The observer watches for the passive emptying of a hiatal hernia.
5. In practicing progressive physiologic insufflation the passage of gas through the cardia is watched for, with especial search for a small persistent pocket of gas which denotes a hiatus hernia.
6. Intermittent hiatal hernias can often be picked up in the course of esophageal reflux.
7. A search is made for the various types of peptic esophagitis, including early stages, sclerosis and peptic ulcers.
8. Search is made for neoplasia.
9. Any malposition is noted.
10. Finally there is a dynamic study of the upper gastric pole.

Although the latter does not have its own motility it can be animated by progressive physiologic insufflation, thereafter evaluating it from the play of the diaphragm, and by varied positioning of the patient.—*Frank A. Riebel, M.D.*

Felix, R., Thurn, P., Düx, A., Winkler, C., Geisler, P., Boldt, C., and Akhtar, M. Vergleichende Wertung des Informationsgehalts von Pulmonalisangiogramm, Lungenszintigramm und Blutgasanalyse. (Comparative evaluation of information gained from pulmonary angiography, pulmonary scintigraphy and blood-gas analysis.) *Fortschr. a. d. Geb. d. Röntgenstrahlen u. d. Nuklearmedizin*, 1967, *107*, 585–600. (Address: Dr. R. Felix, Institut für Röntgenologie und Strahlenheilkunde der Universität, 53 Bonn-Venusberg, Germany.)

Pulmonary angiography, scintigraphy and blood-gas analysis represent a variety of morphologic and functional methods to investigate the lesser circulation. Angiography demonstrates morphologic changes of pulmonary vessels. Scintigraphy aids in the diagnosis of pulmonary emboli and tumors, and blood-gas analysis helps in determining the alveolo-vascular reflex. For the comparative and critical evaluation, all 3 tests must be performed simultaneously in the same patient under identical patho-physiologic conditions.

Patients suffering from bronchogenic carcinoma were tested prior to pneumonectomy. They were elderly with signs of advanced pulmonary emphysema. Pulmonary angiography was performed under fluothane anesthesia and was followed by functional elimination of the tumor-lung while the healthy lung received oxygen. At 5, 10 and 15 minutes, samples of arterial and mixed venous blood were taken. This was followed by control angiography and scintigraphy. Five minutes later the function of the eliminated lung was restored.

The characteristic changes are illustrated in 4 representative cases.

The pulmonary scintigram yields information regarding changes of blood flow in both lungs. While it discloses regional distribution of the blood flow, it does not indicate the cause and location of increased hemodynamic resistance unlike angiography. The limited value of scintigraphy must be considered in the interpretation of so-called sequestration defects. Increased defects can be produced by functional elimination of the overlying lung. Pulmonary angiography appears superior to scintigraphy and blood-gas analysis, but all 3 methods when used simultaneously contribute to the clarification of problems of the lesser circulation.—*Ernest Kraft, M.D.*

Hennig, K., Woller, P., and Franke, W. G. Erfahrungen bei der Lungenszintigraphie. (Experience with pulmonary scintigraphy.) *Fortschr. a. d. Geb. d. Röntgenstrahlen u. d. Nuklearmedizin*, 1967, *107*, 600–609. (Address: Dozent Dr. med. habil. K. Hennig, Nulkearmedizinische Abteilung der Radiologischen Klinik der Medizinischen Akademie, Carl Gustav Carus, Fetscherstrasse 74, X8019 Dresden, Germany.)

The ideal isotope for performing pulmonary scintigraphy is I^{131}-labeled macroaggregates of human serum albumin. It is stored in the lungs up to 87 per cent of the intravenously injected dose. The authors report their experience in 500 patients. The technique comprises an injection of 200 to 500 μc with the patient supine, to be immediately followed by the scintigraphy.

Peculiarities of the normal scintigram are unsharp and irregular lower borders due to respiratory motion. The heart causes a partial obliteration of the left lower lung field; therefore, left basal lesions can be easily obscured. The position of the patient also modifies the results. Storage in the apical fields, for example, is diminished when the injection is done with the patient erect. In the lateral decubitus position, the dependent lung exhibits more activity than the contralateral lung.

Pathologic conditions cause simple defects due to circulatory, vascular or parenchymal changes. In

view of the numerous causes of abnormalities, the scintigram has no pathognomonic features but merely supplements roentgenologic and other diagnostic procedures. In vascular lesions, it can be more informative than the roentgenogram especially when the pulmonary artery is stenosed. It also is very helpful in the diagnosis of emboli, cysts, and emphysema, and aids in differentiating tuberculous lesions and bronchogenic carcinoma. Small solitary, noninfiltrating lesions may not be registered when the supine position is unfavorable for scanning. In such instances, the prone or lateral position can prove superior.

Scintigraphy is indicated to test the extent of diminished pulmonary function, to differentiate expansile and infiltrative processes in the hilus and mediastinum, and to determine vascular changes when chest roentgenograms are noncontributory.

It is concluded that pulmonary scintigraphy is distinctly valuable. It is a simple procedure, nonhazardous and free from side-effects.—*Ernest Kraft, M.D.*

Fabel, H., Kunitsch, G., and St. Stender, H. Störungen der Lungenfunktion nach Lymphographie. (Disturbances of pulmonary function following lymphography.) *Fortschr. a. d. Geb. d. Röntgenstrahlen u. d. Nuklearmedizin*, 1967, *107*, 609–618. (Address: Priv. Doz. Dr. H. Fabel, Medizinische Klinik, Institut für Klinische Radiologie der Med. Hochschule, Podbielskistrasse 380, 3000 Hannover, Germany.)

Lymphography is considered a rather innocuous procedure although the opaque oil flows via the thoracic duct into the lesser circulation. Potential side-effects are minimized due to its great diagnostic and prognostic value. Only in rare instances can oil embolization be visualized in roentgenograms of the lungs. Actually, however, microembolization occurs regularly and deserves serious consideration. The extent of ensuing impairment of pulmonary function can only be determined by blood-gas analysis combined with serial roentgen studies.

For their investigation, the authors selected 30 patients with normal lungs out of a total of 450 lymphographic studies. Ten patients received 15 to 20 ml. and the remaining 20 patients, only 12 to 14 ml. Lipiodol UF (ultrafluid). Blood-gas analyses, comprising arterial O_2 saturation (pO_2) and arterial pH values were determined at the beginning of the infusion and 4 as well as 24 hours afterward. When the 24-hour study disclosed a continued depression of the O_2 pressure, a 48-hour analysis was added. Serial roentgen studies were also done simultaneously.

The roentgen findings were grouped into three different stages. In the first stage, at 4 and 24 hours, there always appeared miliary densities caused by superimposition of microemboli. The second stage was characterized by larger densities and the third stage by more advanced changes. These included perivascular and peribronchial interstitial changes with interlobular septal lines of Kerley.

In 6 out of the 10 patients who had received the larger dose of lipiodol the arterial pO_2 was markedly depressed after 4 and 24 hours, only to become restored to the original value after 48 hours. The pH values increased proportionately and roentgenographic changes belonged to the second and third stage. When only 12–14 ml. lipiodol was infused, all changes were much less pronounced and quickly restored to findings prevailing prior to the infusion.

It is estimated that an amount of 20 ml. lipiodol results in approximately 40 million pulmonary microemboli. An unknown quantity, however, remains stored in the lymph nodes. In view of the effect on the lesser circulation, the opaque oil has to be reduced to the smallest effective dose. The ml. is considered the absolute minimum for an adequate study, while too small a dose tends to be misleading. An amount of 12 to 14 ml. is considered sufficient with 12 ml. to be used in older and 14 ml. in younger patients.

Lymphography is definitely contraindicated in patients with diminished pulmonary function. Diagnostic and therapeutic measures must be guarded against during the first few days following the procedure, as well as operations and anesthesias.—*Ernest Kraft, M.D.*

Levin, David C. The "P.I.E." Syndrome—Pulmonary Infiltrates with Eosinophilia: a report of 3 cases with lung biopsy. *Radiology*, Sept., 1967, *89*, 461–465. (From: Department of Radiology, UCLA Center for the Health Sciences, Los Angeles, Calif. 90024.)

The term P.I.E. syndrome has been suggested to designate a disease which is similar to Loeffler's syndrome but is more virulent and potentially life threatening. Loeffler's syndrome classically consists of transient, mild pulmonary infiltrations, blood eosinophilia, and a benign clinical course. Patients with the P.I.E. syndrome may experience protracted symptoms with recurrent episodes of severe weakness and debilitation, weight loss, daily temperature fluctuations, cough, hemoptysis, dyspnea, and chest pain. Chest roentgenograms show diffuse shifting infiltrates of a coarse, ragged, mottled nature which persist in spite of antibiotic therapy. No single specific etiologic agent has ever been found.

The author presents case reports of 3 patients with severe and protracted pulmonary infiltration with eosinophilia. These cases illustrate the variety of clinical courses which the P.I.E. syndrome may take. All were substantiated by lung biopsy. Administration of steroids produced dramatic clinical and roentgenographic improvement.—*A. W. Sommer, M.D.*

CATES, G. W., and ROBINSON, CLAYTON L. N. Angiofollicular mediastinal lymph node hyperplasia. *Canad. M. A. J.*, Dec. 16, 1967, *97*, 1538–1541. (Address: G. W. Cates, M.D., Professor of Pathology, University of Saskatchewan, Saskatoon, Sask.)

The case of a 40 year old female with a right hilar mass, unchanged for 21 years, is reported and discussed. Surgical removal revealed a localized mediastinal lymph node hyperplasia resembling a thymoma. Harrison and Bernatz in 1963 called this lesion, "angiofollicular lymph node hyperplasia."

The nature of this lesion is contoversial. Most investigators believe that it is benign. Some authorities consider it a chronic, nonspecific lymphadenitis and others a benign neoplasm. The lesion does not recur even after incomplete removal.—*John H. Harris, M.D.*

REES, R. S. O., and JEFFERSON, K. E. The Eisenmenger syndrome. *Clin. Radiol.*, Oct., 1967, *18*, 366–371. (From: The National Heart and St. George's Hospitals, London, England.)

A combination of cyanosis and ventricular septal defect since first described by Eisenmenger in 1897 has been called the Eisenmenger complex. However, severe pulmonary hypertension is always present, and is productive of the reversed shunt producing central cyanosis. Wood in 1958 suggested that the term Eisenmenger syndrome should be used in describing all cases of pulmonary hypertension with the reversed shunt, regardless of the site of the defect.

The authors studied the plain chest roentgenograms of 81 patients with the Eisenmenger syndrome. They conclude that the plain chest roentgenogram may be very helpful in localizing the level of the shunt. Atrial septal defect presents large main and lobar arteries, an abrupt reduction in size at segmental artery level, a small aorta, tendency to gross cardiac enlargement and displacement of the heart to the left. The absence of abrupt changes in artery size and the relatively normal appearance of cardiac silhouette and lung fields, especially in children with the Eisenmenger syndrome, suggest a ventricular septal defect. A patent duct is suggested by a characteristic aortic knuckle, and a vessel pattern similar to that seen in ventricular septal defect, although the majority of such cases present gross main pulmonary artery enlargement.

In all groups the heart tends to increase in size with age. Scoliosis was noted in 8 out of 27 patients with atrial septal defect, but was seen only twice in association with patients with a patent duct, or with interventricular septal defect.—*Samuel G. Henderson, M.D.*

ABDOMEN

MARSHAK, RICHARD H. Roentgen features of granulomatous colitis. *Bull. New York Acad. Med.*, Oct., 1967, *43*, 910–923. (From: Mount Sinai School of Medicine, New York, N. Y.)

The author describes the characteristic roentgen features of granulomatous colitis as seen on the barium enema examination.

The earliest changes are irregular nodules along the contour of the colon associated with slight rigidity and thickening of haustral markings.

Later changes are longitudinal ulcerations, transverse fissures, deep ragged ulcerations, eccentric involvement of the wall, pseudodiverticula, pseudopolypoid changes producing a cobble-stone mucosal pattern and internal fistulae and sinus tracts. Skip areas of involvement are common.

Twelve roentgenographic reproductions are included to demonstrate the features of granulomatous colitis.—*John H. Harris, M.D.*

SHEEHAN, RICHARD G., NECHELES, THOMAS F., LINDEMAN, ROBERT J., MEYER, HEIDI J., and PATTERSON, JAMES F. Regional enteritis and granulomatous colitis associated with erythrocyte glucose 6 phosphate dehydrogenase deficiency. *New England J. Med.*, Nov. 23, 1967, *277*, 1124–1126. (From: The Hematology Research Laboratory, Boston Floating Hospital of New England Medical Center Hospitals, and the Department of Pediatrics and Medicine, Tufts University School of Medicine, Boston, Mass.)

Forty-two unrelated persons with regional enteritis, 11 patients with granulomatous colitis and 50 patients with ulcerative colitis were reviewed by the authors in relationship to erythrocyte glucose 6 phosphate dehydrogenase deficiency (G 6 P D).

Fifty-three patients with regional enteritis and granulomatous colitis revealed erythrocyte G 6 P D deficiency in 9.6 per cent. None of the 50 patients with ulcerative colitis had this defect.

Northeastern European Jewish extraction persons comprised 50 per cent of the regional enteritis cases, 40 per cent of the granulomatous colitis cases, and 27 per cent of the ulcerative colitis cases.

Of the 5 apparently unrelated persons with erythrocyte G 6 P D deficiency associated with regional enteritis or granulomatous colitis, all were of Ashkenazic Jewish origin from an area of Russia-Poland centering on the city of Vilna. A total of 4 additional family members were found to have both defects in 2 of the 5 families.

The authors point out that several of the drugs used commonly to treat regional enteritis may cause marked hemolysis if severe erthrocyte G 6 P D is present. They suggest testing all patients with

[illegible] atous disease of the bowel, especially in the [illegible]al form.—*George A. Miller, M.D.*

Boijsen, Erik, and Reuter, Stewart R. Angiography in diagnosis of chronic unexplained melena. *Radiology*, Sept., 1967, *89*, [illegible]–19. (Address: S. R. Reuter, Wayne County General Hospital, Eloise, Mich. 48132.)

Selective celiac and superior mesenteric angiography was performed in 24 patients with chronic melena in whom previous gastrointestinal barium examinations failed to reveal the bleeding source. Vascular abnormalities were seen in 22 of these patients, but few were of the type generally associated with melena.

Possible mechanisms of bleeding in the various abnormality groupings are discussed.

Of those patients with positive findings, 10 had occlusive disease of the celiac axis or its main branches with collateral flow through the pancreaticoduodenal arcades, 4 had mesenteric circulation abnormalities, 3 had a small bowel leiomyoma, 2 had major venous channel compression by tumor with resultant portal hypertension, and 5 had hypervascular segments of the stomach or duodenum. Two patients had 2 of the above conditions concomitantly.

The authors reiterate an interesting concept in support of "old age ulcers" on the basis of gastric ischemia secondary to occlusive disease of the celiac axis or its branches.—*V. Brasseur, M.D.*

Gynecology and Obstetrics

Slezak, P. Intrafetal gas. *Radiology*, Nov., 1967, *89*, 878–880. (Address: P. Slezak, Röntgendiagnostiska Institutionen, Karolinska Sjukhuset, Stockholm 60, Sweden.)

The roentgenograms taken in 53 cases of intrauterine death were reviewed and analyzed. All patients were examined by Edholm's method to investigate: (a) the incidence of extravascular gas; (b) whether it is possible to distinguish intrafetal gas from maternal gas or from translucent tissue such as fetal fat; and (c) whether it is possible to determine roentgenographically in which vessels the gas is contained.

With Edholm's method the maternal intestines are displaced and not superimposed on the fetal shadows, thereby permitting a differential diagnosis between intrafetal and maternal gas.

Extravascular gas was detected in only 2 cases and was seen to be present in the vertebral canal in both. Blood vessels were usually easy to identify but it was difficult to ascertain whether the gas was in the arteries or veins.

It was possible to determine whether the gas was present in the arteries or veins in the fetal thorax, pelvis, and thigh but not in the lower abdomen.

Differential diagnosis between intrafetal and maternal gas was not difficult.—*A. W. Sommer, M.D.*

Buchet, R. (Paris, France.) Le lithopédion. Rarissime (masse) pelvi-abdominale: discussion diagnostique et revue générale. (Lithopedion; a rare pelvic-abdominal mass: diagnostic discussion and general review.) *J. de radiol., d'électrol. et de méd. nucléaire*, Oct., 1967, *48*, 537–548.

A 78 year old woman complained of rectal bleeding, the apparent cause of a prolapse. However a low-lying pelvic mass double the size of a grapefruit was palpated, and roentgen investigation showed a calcified fetus and membranes of 6 months' size. The patient had been aware of the mass for 40 years and recalled that at the age of 29 years she was amenorrheic for 7 months.

Lithopedion is a rare condition, this being the 264th case in the literature. It results from ectopic pregnancy, and develops in cases, wherein there is an absence of infection and the amniotic fluid is resorbed. Thereafter the cyst slowly retracts, and the fetus degenerates, mummifies and then calcifies. Usually the amniotic membrane is resorbed, although, as in this case, it may calcify.—*Frank A. Riebel, M.D.*

Genitourinary System

Clark, Max D., Eyler, William R., Du Sault, Lucille A., Kochkodan, Eugene J., and Caldwell, John R. The renogram in hypertension. *Radiology*, Oct., 1967, *89*, 667–675. (Address: W. R. Eyler, M.D., The Henry Ford Hospital, Detroit, Mich. 48202.)

There has been considerable discussion about the accuracy and interpretation of the isotope renogram, which has often been evaluated on the basis of other examinations such as arteriography, the Howard test, and the excretory urogram. The present study was undertaken to evaluate the renogram by the more definitive criteria of study of resected tissue and the one-year postoperative follow-up of patients undergoing definite procedures. After a review of approximately 3,500 renograms, 52 patients met these criteria.

The technique for a reliable examination is demanding and any deviation from routine will lead to inaccurate interpretation. All patients are examined in the prone position with head of the table elevated 30 degrees to promote drainage by gravity. A moderate dehydrated state is used in that no food or fluid is allowed after midnight, prior to the examination, and the study itself is performed only between the hours of 8 and 12 in the morning. Ideally, the patient is off all antihypertensive medication, especially

those of the diuretic type. At the time of the examination, 1 μc I^{131} orthoiodohippurate (hippuran) is administered for each 8 kg. of body weight.

When the above technique is followed, an ideal normal renogram displays several characteristic features. After an initial deflection the accumulation phase of the renogram rises at least one third of the deflection to a peak which occurs $2\frac{1}{2}$ to 4 minutes after the injection. The descending limb becomes concave upward for most of the 5 minutes following the peak. The renogram of the 2 kidneys should be symmetric and show approximately equal concentration with the peaks not more than $\frac{1}{2}$ minute apart, and the descending limbs of the same shape. Simultaneous recording from a probe placed over the shoulder or head is desirable to permit estimation of total renal function. The tracing should be consistent within itself, in that normal peak times are associated with a normal shape of the descending limb. Similarly, a delayed peak should be associated with delayed descent and resultant straightening or convexity of the descending limb. The most common cause of inconsistency is poor probe position.

The authors emphasize that the isotope renogram should be compared to the normal rather than simply comparing the two sides. The renogram detects bilateral abnormalities whether symmetric or not and no other commonly used test offers this possibility.

Renograms can be categorized and used to predict the possibility of cure of hypertension as follows: 1. (0/52) both sides normal: no such cases were encountered in this series due to the criteria and absence of false negatives; 2. (7/52) one side normal, one side abnormal: the most favorable surgically curable situation with improvement of blood supply to or removal of the ischemic kidney; 3. (14/52) both sides abnormal but symmetric: in this series symmetrically abnormal tracings have indicated diffuse arteriolar nephrosclerosis, glomerulonephritis, coarctation of the aorta or renal shutdown; 4. (31/52) both sides abnormal but asymmetric: various combinations of major and small artery (*i.e.* nephrosclerosis) disease may be present. These cases are also potentially curable depending on the combination of lesions.

No false negative renograms were encountered in the series presented and the authors conclude that renography is a safe and useful procedure for the evaluation of patients with hypertension.—*Edward B. Best, M.D.*

Skeletal System

Beals, Rodney E. Auriculo-osteodysplasia: a syndrome of multiple osseous dysplasia, ear anomaly, and short stature. *J. Bone & Joint Surg.*, Dec., 1967, *49A*, 1541–1550. (Address: Rodney E. Beals, M.D., 3181 S.W. Sam Jackson Park Road, Portland, Oregon 97201.)

Two families with a syndrome of multiple osseous dysplasia associated with characteristic ear anomaly, short stature, and transmitted by autosomal dominant inheritance, are reported. Dysplasia of the radiocapitellar joint with or without radial head dislocation is the constant skeletal feature.

Vertical transmission of the syndrome through the generations is shown which is consistent with dominant inheritance. Passage from father to son rules out X linked inheritance and existence of females with syndrome rules out Y linked inheritance. The syndrome therefore appears to be non-sex linked. The gene is completely penetrant but has variable expression.

Elbow dysplasia (capitellum) with or without radial head dislocation was present in all affected members of both families.

Hip dysplasia or dislocation is reported in 4 of 13 affected females in the 2 families and in none of the males.

Affected members of the 2 families had a masculine appearance to the torso with wide muscular base of the neck, broad shoulders and horizontal clavicles. Roentgenograms of the scapula showed enlargement of the base of the acromion, the axillary border was concave and often scalloped, and the superior medial angle of the scapula was elongated to a palpable prominence.

No apparent abnormality of wrists on physical examination was detectable; however, roentgenograms demonstrated consistent ulnarward sloping of the distal part of the radius as well as lack of normal volar tilt of the distal radius. Some had short metatarsals.

Auricular dysplasia consists of elongation of the lobe of the ear which is attached and accompanied by a small slightly posterior lobule. While this varied in severity it distinguished affected members in both families and was present at birth in the single newborn examined.

The differential diagnosis of congenital dislocation of the radius occurring as an isolated event, as well as the various skeletal and soft tissue syndromes with which this is associated, is considered.

The author believes that the syndrome is best classified as a form of chondroectodermal dysplasia.—*Richard T. Browne, M.D.*

Roze, R., Mazabraud, A., and Semat, P. Dysplasie fibreuse des os et myxomes des tissus mous. Dégénérescence sarcomateuse localisée. (Fibrous dysplasia of bone and myxomas of soft tissues. Localized sarcomatous degeneration.) *J. de radiol., d'électrol. et de méd. nucléaire*, Oct., 1967, *48*, 527–535. (From: Service de Radiologie and Laboratoire d'Anatomie Pathologique du Centre Médico-Chirurgical Foch à Suresnes, France.)

The authors report a case of a female, aged 72

[illegible] with long standing extensive fibrous dys-[illegible] sarcomatous degeneration, and the develop-[illegible] of myxomatous tumors closely apposed but not [illegible] to osseous lesions.

A survey of the literature disclosed 8 similar cases. [illegible] the osseous lesions preceded the musculo-tendinous myxomas by several years, with the soft [illegible] components variable in size and number. In certain cases there were café au lait spots, which makes it important to differentiate from neuro-fibromatosis.

These 9 instances of myxomas of soft tissues (generally musculo-tendinous or aponeurotic) are associated with osteitis fibrosa, or a Jaffe-Lichtenstein fibrous dysplasia; or perhaps they should be individualized as a syndrome in the framework of fibrous dysplasia.—*Frank A. Riebel, M.D.*

HUNT, D. D., PONSETI, I. V., PEDRINI-MILLE, ANGIOLA, and PEDRINI, V. Multiple epiphyseal dysplasia in two siblings: histological and biochemical analysis of epiphyseal plate cartilage in one. *J. Bone & Joint Surg.*, Dec., 1967, *49A*, 1611–1627. (Address: D. D. Hunt, M.D., University of Iowa, Iowa City, Iowa 52240.)

Multiple epiphyseal dysplasia, a hereditary disorder, is reported in two siblings with slip capital femoral epiphysis. One patient had an osteogenic sarcoma of the femur.

This entity is not to be confused with Morquio's disease as urinary mucopolysaccharides are within normal limits while in Morquio's disease a high urinary keratosulphate level is obtained.

The parents gave no history of consanguineous marriage and one other sibling is reported as entirely normal. The family background listed no evidence of dwarfism.

A report is made of the method and result of histologic studies on the amputated specimen. Biochemical analysis was also carried out on the amputation specimen as well as urinary samples from both patients. The methods and results are reported.

The biochemical studies suggest an abnormality in chondroitin sulfate of the growth plate cartilage.

The microscopic studies are reported and show a paucity of chondrocytes in all zones of the growth plate. Maturing cells were distributed in clumps with a complete loss of the normal axial orientation. Columns that had formed contained few cells. The vascular invasion along the epiphyseal side of the plate was uneven. Two types of abnormal calcification are described in the matrix. The calcified matrix, however, formed bone without difficulty when it reached the zone of primary spongiosa. Remodeling appeared to be normal with respect to osteoblast as well as osteoclast activity.

The authors state that this is the first report of slipped capital femoral epiphysis in this entity. They suggest that the slip may be due to the structural and chemical abnormalities of the plates as described above.—*Richard T. Browne, M.D.*

HANLEY, W. BRIAN, MCKUSICK, VICTOR A., and BARRANCO, FRANK T. Osteochondritis dissecans with associated malformations in two brothers: a review of familial aspects. *J. Bone & Joint Surg.*, July, 1967, *49A*, 925–937. (From: The Division of Medical Genetics, Department of Medicine, and Division of Orthopedic Surgery, Johns Hopkins University School of Medicine, Baltimore, Md.)

A review of the pertinent literature is presented by the authors pointing out that there are probably two types of osteochondritis dissecans. The one may occur in adults and older children, trauma being the major or sole cause. The other type occurs in children before epiphyseal closure. Many joints may be involved in this latter type and may be associated with other froms of osteochondritis. Familial occurrences are also found.

Two additional cases are presented of 2 brothers with multiple joint involvement. These brothers were somewhat unusual in that they showed in addition to osteochondritis dissecans numerous developmental abnormalities including a striking facial appearance, congenital ptosis of the eyelids, peculiar pinnae, fusion of the manubriosternal joint with pectus excavatum, cryptorchidism and short fifth fingers and toes. The elder boy was eunuchoid. The younger child had camptodactyly and partial syndactyly.

The authors felt that the osteochondritis dissecans in their patients was probably secondary to developmental abnormalities which were the result of a single gene.—*George A. Miller, M.D.*

HIGHMAN, J. H. Congenital osseous rubella. *Clin. Radiol.*, Oct., 1967, *18*, 445–449. (From: Paddington Green Children's Hospital, Paediatric Unit, St. Mary's Hospital, W.2, London, England.)

Rubella occurring in the first trimester of pregnancy affects fetal development, resulting in congenital heart disease (usually a patent ductus arteriosus), deafness, cataract and mental retardation. An epidemic of rubella occurred early in 1964 in the U.S.A. A series of papers described new aspects of congenital rubella, the result of continuing active infection in the infant. The rubella virus could often be isolated from the throat, urine and viscera, and several contact cases of rubella occurred in nurses caring for these infants. Various authors noted low birth weight, thrombocytopenic purpura, hepatosplenomegaly, pulmonary consolidation, myocarditis and bone changes, in addition to the usual evidence of cataract, deafness, mental defect and congenital

cardiovascular disease. The bone changes occur at the metaphyses, particularly at the knee, and consist of a "moth-eaten" irregularity of metaphyseal contour, a translucent metaphyseal band, and alternating sclerotic strands and translucent strands perpendicular to the metaphysis. The bone changes are of short duration and regress to a normal appearance within a few weeks after birth.

Two cases of congenital rubella are described by the author. In Case I the newly recognized syndrome of congenital rubella was apparent when a positive rubella neutralizing antibody titer of 1:28 was found at the age of 8 months. Roentgenographic examination the day after birth showed the lower femoral metaphyses to be irregular in the zone of provisional calcification, and the long bones of the legs showed a coarsening and irregularity of trabecular structure of the shafts. A metaphyseal erosion was noted at the upper end of the right humerus. Roentgenographic examination at 4 months revealed a fine sclerotic band at the distal ends of the radii and ulnae, tibiae and fibulae, and eventually the bone texture became completely normal in appearance. The child also had a patent ductus arteriosus, severe deafness and psychomotor retardation.

In Case II the rubella neutralizing antibody titer was over 1:256 in the mother's serum, and 1:256 in that of the child. On roentgenographic examination the femora showed failure of modeling distally, cortical thinning and loss of trabecular definition, suggestive of Gaucher's disease. Rubella virus was grown from the nasopharnyx and urine. This child had, in addition, a persistent ductus arteriosus, a cataract in the left eye, psychomotor retardation and an abnormal distribution of immunoglobulins.

The author believes that in practice it is likely that congenital rubella will now be a more frequent cause for the described changes than congenital syphilis.—*Samuel G. Henderson, M.D.*

Ghislanzoni, R., and Santolini, B. M. Contributo allo studio del granuloma esosinofilo dello scheletro, a localizzazioni multiple. (Contribution to the study of the eosinophilic granuloma of the skeleton, with multiple localizations.) *Radiol. med.*, 1967, *53*, 641–652. (From: Istituto di Radiologia dell'Università di Genova and Istituto Ortopedico Elioterapico, San Giorgio, Genova, Italy.)

Two cases of eosinophilic granuloma with multiple skeletal localizations are reported.

The authors follow the theory which groups eosinophilic granuloma, Hand-Schüller-Christian disease and Letterer-Siwe disease under one nosologic unity.—*A. F. Govoni, M.D.*

Rinaldi, A. Biolcati. L'osteolisi progressiva criptogenetica: rassegna della letteratura e presentazione di un nuovo caso. (Progressive cryptogenetic osteolysis: review of the literature and presentation of a new case.) *Ann. radiol. diag.*, 1967, *40*, 263–296. (From: Istituto di Radiologia e Terapia, Università degli Studi di Ferrara, Ferrara, Italy.)

A case of progressive massive osteolysis involving the right lower limb is reported.

The patient, a female 13 years of age, was first seen at the age of 2 years for a deformed right foot. Roentgen studies demonstrated hypoplastic metatarsal bones, with deformed, and somewhat irregular contours, and diffuse, moderate demineralization of the component bones of the foot.

Through the years, successive roentgen studies of the right foot, then of the tibia and fibula and, finally, of the femur and right hemipelvis, showed the slow progress of the process of osteolysis.

Arteriographic and lymphangiographic studies were within normal limits and so were the histologic studies from biopsies taken, on two different occasions, from the metatarsal bones and from the pelvis.

In reviewing the literature the author found 55 cases of massive osteolysis of bone, mostly in the second and third decades of life. In 23 patients in whom biopsy and histologic studies were performed, angiomatous lesions were demonstrated in the bone involved.

In the opinion of the author the disease is secondary to neurotrophic disorders of the bone metabolism.—*A. F. Govoni, M.D.*

Dellipiani, A. W., and George, M. Syndrome of sclerodactyly, calcinosis, Raynaud's phenomenon, and telangiectasia. *Brit. M. J.*, Nov. 11, 1967, *2*, 334–335. (From: The Department of Therapeutics, The Royal Infirmary, Edinburgh 3, Scotland.)

This syndrome when compared with the originally described association between scleroderma and calcinosis (Thibierge-Weissenbach syndrome) is much more benign. From 1954 to 1964, only 25 cases have been reported. In the present report the authors describe 3 further cases, all females.

In each case the component parts of the syndrome were well demonstrated. It is noted from the present cases and a review of previous cases that telangiectasia in this condition is not hereditary, predominantly affects females, and has a wide age distribution which on the whole usually occurs later than in the hereditary condition.

The occurrence of signs of systemic scleroderma in the syndrome is discussed. It should be emphasized that this type of scleroderma tends to run a relatively benign course and that the progression of the disease is slow even in the presence of such systemic involvement.—*John E. Jenkins, M.D.*

GOLDENBERG, RAPHAEL R., COHEN, PHILIP, and STEINLAUF, PAUL. Chondrosarcoma of the extraskeletal soft tissues: a report of seven cases and review of the literature. *J. Bone & Joint Surg.*, Dec., 1967, *49A*, 1487–[illegible] (Address: Raphael R. Goldenberg, M.D., [illegible]28 East Twenty-seventh Street, Paterson, N. J. 07504.)

Cartilaginous soft tissue tumors completely detached from bone or cartilage, were first described in 1870 by Paget. These lesions are usually small, less than 2 cm. in size, and benign in nature. The paucity of reports as regards malignant lesions of this nature in the literature lends support to its rarity. The lack of published cases of this entity as well as its exclusion from some pathologic textbooks further support the rarity of the entity.

The purpose of the authors is to review the 19 reported cases and record 7 additional cases of chondrosarcoma arising in soft tissue. It is hoped that the lesion will be better defined and hence more often considered in differential diagnosis of soft tissue tumors. Excluded from this study are teratomas, mesenchymomas, and extraskeletal osteogenic sarcomas. In addition, chondrosarcoma arising from periosteum and normal extraskeletal cartilage such as tracheobronchial tree and nasal passage is excluded.

No definite age group is established in this study; however, the lesion predominates in males approximately 2:1.

Countless sites of origin are reported with most in the gluteal region and lower extremity with only 5 in the shoulder and upper extremity and 1 each in the tongue, thoracic wall, and urinary bladder. The site of origin in muscle or connective tissue is discussed in each case.

In the added cases, as well as those already discussed in the literature, there were no distinctive clinical features and no case was diagnosed clinically. Most common complaints were pain and enlarging mass, the duration of symptoms varying from 3 weeks to 2 years.

The roentgen features are not characteristic. Suggestive diagnosis could be made when evidence of a soft tissue mass containing spotted areas of radiopacity is identified. It was not always possible, however, to visualize a soft tissue mass and calcification was not necessarily present. These lesions may erode or directly invade the bone.

No report is made of malignant degeneration of a benign cartilaginous tumor of soft tissue origin. It is probable that extraosseous chondrosarcomas arise *de novo* rather than from pre-existing benign chondromas.

Rather extensive discussion is given to the microscopic pathology of the tumor including the ominous signs of high cellularity as well as large size of the lesion. Speckled calcification was frequently identified in the tumors even when not visible on roentgenograms.

The difficulty of differentiating a parosteal or a para-articular chondroma from an extraskeletal chondrosarcoma by microscopic examination is noted.

Recurrences as well as metastases are reported. The time of recurrence was as early as 2 months and as late as 15 years postoperatively. While metastases were less prominent, they are reported and these features make long term follow-up essential.

The treatment of choice is by block resection which is the only form of therapy which offers a prospect for cure. Excisional biopsy is preferable to incisional biopsy because of the danger of implantation of viable malignant cells. The fact that metastases are somewhat uncommon permits the surgeon to attempt wider local excision of the primary tumor with hope for cure. When the tumor has recurred or invaded bone, amputation should be carried out. There are no reported cures of extraskeletal chondrosarcoma by radiation therapy.

The tendency for local recurrence means that prognosis must be considered as guarded and close follow-up must be obtained in these cases.—*Richard T. Browne, M.D.*

SILBERMAN, FERNANDO S., KHOURY SOLÁ, CARLOS, and CABRINI, RÓMULO L. A study of the vascular distribution after periosteal stripping of the long bones. *Surg., Gynec. & Obst.*, Dec., 1967, *125*, 1311–1315. (From: The Dupuytren Institute, Buenos Aires, Argentina.)

The authors utilized 40 dogs in their study. Nine of these were used as control and 31 had periosteal stripping. In 9 of the stripped animals, a sheet of polyethylene was wrapped around the bone and placed between the bone cortex and the periosteum to prevent any attempt on the part of the periosteum toward vascular regeneration. One dog each was sacrificed at 1, 2, 3 weeks, 2 months, 2½, 3½, 4½ months until 1 year.

They studied the vascularization by injection of micropaque in the aorta or carotid artery in an isotonic solution with the addition of formalin. Roentgenograms were taken of the whole bone first, and also in .05 cm. sections after decalcification in nitric acid.

The authors observed total absence of vascular paths in all diaphyseal zones, 7 days after stripping. There was slight decrease of endochondral vascularization in the metaphysis. Revascularization of the whole diaphysis started at about 21 days. Increased vascular pattern was also noted in the enchondral area. From 2 months onward, the diaphysis had a well-developed vascularized pattern which was more

pronounced than that seen in the control group. This pattern, however, was different from the normal characteristic bipolar penicillate distribution of the blood vessels.

The group that had a polyethylene sheet between the periosteum and cortex in growing bones showed complete absence of the vascularization in the diaphyseal area and necrosis systematically developed. On the other hand, the adult bones treated in the same manner showed persistence of diaphyseal vascularization possibly at the expense of the epiphyseal-diaphyseal communication, as the epiphyseal plate no longer existed. One month after operation, the vascular pattern almost approached that of normal.

The authors believe that a relationship is evident between the stimulation of longitudinal growth and the increased vascularization in the areas corresponding to the metaphyseal zone.—*Gonzalo Chua, M.D.*

Bloom, Marvin H., and Obata, William G. Diagnosis of posterior dislocation of the shoulder with use of Velpeau axillary and angle-up roentgenographic views. *J. Bone & Joint Surg.*, July, 1967, *49A*, 943–949. (From: The Department of Orthopaedic Surgery, University of California School of Medicine, San Francisco, and the Department of Radiology, Franklin Hospital, San Franciso, Calif.)

Posterior dislocation of the shoulder accounts for 2–4 per cent of all shoulder dislocations. Reports indicate that up to 50 per cent of such injuries are not initially recognized. Such delays may necessitate open reduction.

Standard and many of the special views of the shoulder which may help to make a correct diagnosis are at times misleading or almost impossible to obtain.

The authors propose examination in 2 new views which can be done without removal of the immobilizing bandage and provides direct evidence of posterior dislocation.

Velpeau Axillary View. "With the bandage or sling in place, the patients stand or sit at the edge of the roentgenographic table and lean 20–30 degrees backwards over the table. The cassette is placed on the table directly beneath the shoulder. The roentgen tube is placed over the shoulder so that the rays project vertically downward through the shoulder to the cassette."

Angle-Up View. "This view can be done standing, seated, or supine. The cassette is held parallel to the long axis of the thorax and posterior to the shoulder joint. Bandages need not be removed. The roentgen tube is angled cephalad approximately 35 degrees to direct the central ray obliquely through the joint to the cassette."

The article is well illustrated with case histories, diagrams and roentgenographic reproductions.—*George A. Miller, M.D.*

Blood and Lymph System

Fegan, W. G., and Doporto, M. The chronically swollen leg. *Brit. J. Surg.*, Oct., 1967, *54*, 895–898. (From: Sir Patrick Dun's Hospital, Dublin, Ireland.)

Compression sclerotherapy in the treatment of postphlebitic limbs, even those with proximal obstruction, has been used at two Dublin Hospitals for 16 years on 18,000 patients, over 3,000 of whom have had chronic stasis edema.

Underlying successful management in these cases is a meticulous clinical examination to locate each incompetent perforating vein. Elastic bandage wraps to reduce edema prior to examination and occasionally phlebography are also used to evaluate the limb. Subsequently a sclerosing agent is injected into the incompetent perforating vein to cause intimal damage, thrombus formation and eventually fibrosis and obliteration of a segment of vein.

The authors stress that three factors are essential for the successful employment of this method. *First*, compression must be adequate and uninterrupted in order to prevent retraction of the venous wall from the thrombus and thereby prevent a recurrent lumen from forming. *Second*, ambulation is used to stimulate rapid organization of a mature fibrous occlusion. In addition, this allows the patient to continue his occupation and hospitalization is avoided during the course of the treatment. *Third*, prolonged inactive standing is avoided to prevent stagnant blood accumulation at high venous pressures that tend to separate the thrombus from the venous wall.

The rationale of this treatment is dependent upon the physiology of the venous system. The myofascial compartments of the lower limb are comparable to those of the heart, in that the deep veins and their valves are surrounded by muscle masses that pump the blood to the cardia against gravity. These pumping systems have both pathologic and physiologic reserve capacity. Despite damage to a few deep vein valves the system is able to function. Muscle paralysis or hormone induced relaxation of fascia in pregnancy can, however, overcome this capacity. The ability of the system to handle increased venous blood volume during exercise is considered its physiologic reserve. When the reserve is transgressed signs and symptoms appear. Treatment is designed to return the pumping system to within the limits of the reserve capacity by obliteration of the incompetent perforating veins.

Chronic edema of venous origin may be due to perforating vein incompetence, deep venous valvular incompetence or obstruction of proximal deep veins

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Roentgenographic evidence of damaged deep and perforating veins can usually be demonstrated. Occlusion of incompetent perforating veins prevents blood leakage into superficial veins, increases deep vein pressure and thereby promotes development of collateral circulation.

The authors conclude that compression sclerotherapy even in obstruction, can be a successful method of treatment lending itself to repeated outpatient administration.—*John T. Underberg, M.D.*

Cockett, F. B. Venous causes of swollen leg. *Brit. J. Surg.*, Oct., 1967, *54*, 891–894. (From: The St. Thomas Hospital, London, England.)

The venous causes of swollen leg are discussed as to their etiology and surgical treatment.

Obstruction is classified as resulting from surgical ligature, external pressure due to pathologic conditions, and the iliac compression syndrome combined with ilio-femoral thrombosis.

The amount of swelling in the limb depends on the level of obstruction and the anatomic availability of collaterals. Therefore, when a considerable length of vein is obstructed as in ilio-femoral thrombosis, which the author considers to be due to iliac compression by the left iliac artery, the edema is particularly severe.

Venography is recommended for diagnosis.

The site of compression can be the iliac veins or vein at the crossing of the right common iliac artery or the bifurcation of the common iliac artery. Compression can occur under the inguinal ligament also.

The severity of symptoms depends on the collateral circulation developed and its efficiency. The author recommends measurement of the femoral venous pressure at rest and during exercise. Patients with a rise of pressure usually have severe symptoms.

The selection of patients for operation and the two types of operation, bypass and thrombectomy, are discussed.

As many patients exhibit a compression defect across the left iliac vein on venograms, it is the author's implication that the presence of collaterals is the criterion for the consideration of clinically significant obstruction.—*Roger Pyle, M.D.*

Townsend, Julian, Jones, Hugh, and Williams, J. Edmund. Detection of incompetent perforating veins by venography at operation. *Brit. M. J.*, Sept. 2, 1967, *2*, 583–585. (Address: Dr. Julian Townsend, Senior Surgical Registrar, Varicose Vein Clinic, Cardiff Royal Infirmary, Cardiff, Wales.)

Varicose veins can be treated successfully by a radical stripping operation in which the whole system of diseased veins and related perforating veins is removed. Incompetent perforating veins are easy to overlook clinically and are especially important as a cause of varices that persist or recur after surgery.

The venous drainage of the lower part of the leg ("gaiter-area") is through short perforating veins to the deep vessels, and only indirectly through the saphenous system. High intermittent pressures in the deep veins can be transmitted to the surface via incompetent perforators, leading to varicose ulceration. Stripping the saphenous trunk does not destroy the perforating vein, which must be individually localized and ligated for good long-term results.

The authors describe a method of operative intraosseous venography employed at the Varicose Vein Clinic, Cardiff Royal Infirmary. Injection of 20 cc. of hypaque is made into the tibia above the medial malleolus after the leg veins were drained by raising the leg. Roentgenograms are taken in frontal projection.

Intraosseous venograms are simple to interpret because of the lack of superficial venous filling. Incompetence is almost certain when a perforating vein is seen with localized filling of veins at its superficial end, for then flow must have been outward. An abnormal perforator is enlarged and may be irregular. A localized superficial varix is a strong indication of the presence of an incompetent perforating vein.—*Rosalind H. Troupin, M.D.*

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The author points out that while thrombophlebitis has been reported with moderate frequency, arterial lesions have not. Her patient had aneurysms of both the thoracic and abdominal aortae. At operation the vessels were thick and inflammed and there was also inflammation of the adjacent lymph nodes. The more serious abdominal aortic aneurysm was resected

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and the patient is currently alive and his condition controlled by steroids.

The author presents evidence that this disease belongs to the auto-immune group and she emphasizes that it is not rare in Europe, but the association is missed because patients are not questioned regarding the presence of oral and genital ulcers.—*Roger Pyle, M.D.*

Shepherd, J. J., and Wright, D. H. Burkitt's tumour presenting as bilateral swelling of the breast in women of child-bearing age. *Brit. J. Surg.*, Sept., 1967, *54*, 776–780. (From: Makerere University College Medical School, Kampala, Uganda.)

Burkitt's tumor is a malignant lymphoma affecting mainly children in tropical Africa (*Brit. J. Surg.*, 1958, *46*, 218). The tumor cells have a characteristic morphology permitting identification and separation from other malignant lymphomas.

The age incidence is maximum at 5–8 years, and the disease is uncommon after the age 15 years, thus being unusual in women of child-bearing age. In more than 600 cancer registry patients past 15 years of age, only 17 female patients over the age 15 are recorded. In these 17 cases the most frequent organ affected was the ovary, but involvement of the breast, thyroid, jaw, orbit, spine and intestine was also seen.

This report concerns 5 cases and an addendum of a sixth case of bilateral breast involvement in young females, either in late pregnancy or recently post partum. The predilection for the breast during pregnancy suggests that in the female the distribution of Burkitt's tumor may be estrogen dependent. The only survival in the 6 reported cases was following cessation of lactation.

It is now recognized that cases clinically, anatomically, and histologically identical to Burkitt's tumor occur sporadically in America and England, and that probably some previous reports of bilateral breast lymphosarcoma were in fact Burkitt's tumor.—*Mark D. Reiss, M.D.*

Holt, J. M., Mayet, F. G. H., Warner, G. T., and Callender, S. T. Measurement of blood loss by means of a whole-body counter. *Brit. M. J.*, Oct. 14, 1967, *2*, 86–88. (From: Nuffield Department of Clinical Medicine, Radcliffe Infirmary, Oxford, England.)

A method is described for the measurement of blood loss over periods of up to 3 months using radioactive iron and a whole body counter. The design of the whole body counter is reported elsewhere (listed in the bibliography). The principles involved are that 7 to 10 days after administration of the radioactive iron most of the dose will be incorporated in circulating red blood cells. In normal males and in postmenopausal females whole body radioactivity should remain stable and any loss in the total body radioactivity must represent blood loss.

The technique was evaluated by studying patients with polycythemia who had known amounts of blood withdrawn by venesection.

Clinical use of the technique is illustrated by studies of 5 patients with hypochromic anemia. Accuracy and reproducibility of the method were very limited in blood loss volumes of under 300 ml. Even with loss of 400 to 500 ml. the standard deviation of the errors was 26 per cent. With volumes, however, of between 700 and 3,000 ml. over periods of time ranging from 1 to 97 days the standard deviation of errors declined to 14 per cent. The authors feel that this is sufficiently accurate for quantitative assessment of blood loss in patients with hypochromic anemia over longer periods of time.

The simplicity of the technique allows its use on outpatients.

The authors are currently investigating the mechanism of anemia in patients with hiatus hernia, ulcerative colitis and Crohn's disease as well as offering the procedure in the evaluation of hypochromic anemia generally.—*Everett H. Johnston, M.D.*

RADIATION THERAPY

Strickland, N. J., Bold, A. M., and Medd, W. E. Bronchial carcinoma with hypercalcaemia simulating cerebral metastases. *Brit. M. J.*, Sept. 2, 1967, *2*, 590–592. (Address: Dr. N. J. Strickland, Medical Registrar, Kingston Hospital, Kingston-upon-Thames, Surrey, England.)

A case of hypercalcemia from squamous cell carcinoma of the bronchus is described. The symptoms of hypercalcemia (lethargy, mental disturbance, anorexia and vomiting) resembled those of cerebral metastases. Preoperatively, calcium levels greater than 15 mg./100 ml., with low serum phosphorus and normal serum albumin were noted. The calcium levels returned to normal after removal of the tumor with permanent resolution of the symptoms of cerebral metastases.

The authors note in their review of the literature that bronchial carcinoma (squamous cell type) is the most common neoplasm to cause hypercalcemia in the absence of bone metastasis. Neoplasm induced hypercalcemia may be due to stimulation of the parathyroid glands, tumor production of a parathyroid-hormone-like substance, or to factors unknown. Urinary calcium is not reliable as a guide since this may be either low or high.—*Richard J. Torpie, M.D.*

Fracchia, A. A., Randall, H. T., and Farrow J. H. The results of adrenalectomy in advanced breast cancer in 500 consecutive patients. *Surg., Gynec. & Obst.*, Oct., 1967,

[illegible]6. (From: The Department of [illegible], Memorial Hospital for Cancer and [illegible] Diseases, and the James Ewing [illegible], New York, N. Y.)

Five [illegible]dred consecutive patients with adrenalecto[illegible], o[illegible]ophorectomy and adrenalectomy, for advanced [illegible]ast cancer in the Memorial and James Ewing Hospitals were reviewed.

An objective remission or total arrest of 6 months or longer was achieved in 35.6 per cent of patients. Objective improvement was defined as a measurable decrease in the size of the primary lesion, local recurrence or metastases as well as demonstrable regression of metastatic pulmonary nodules, recalcification of osteolytic skeletal metastases, and no recurrence of pleural effusion.

Selection of patients who have a high probability of responding is important because of the operative morbidity and mortality.

Factors which increase the probability of response include a free interval from initial treatment to first recurrence or metastasis of 2 years or more, a previous response to oophorectomy or irradiation castration in premenopausal women, and an abnormally high vaginal smear index in postmenopausal women.

Factors which should exclude a patient from consideration for adrenalectomy include central nervous system metastases, restrictive pulmonary disease, jaundice, hypercalcemia, (myelophthisic) anemia, pathologic fractures of long bones and sudden outburst of disseminated disease.

Patients with primary inoperable breast cancer, including inflammatory carcinoma, demonstrated a satisfactory remission rate.

Oophorectomy and adrenalectomy should be considered earlier in the course of advanced breast cancer in patients selected on the basis of the factors favoring a response to adrenalectomy.

Other palliative methods of treatment may be effectively employed in both adrenalectomy failures and in responding patients following relapse.—*Robert I. Miller, M.D.*

RADIOISOTOPES

Little, J. M., McRae, J., Smitananda, M., and Morris, J. G. Radioisotope scanning of liver and spleen in upper abdominal trauma. *Surg., Gynec. & Obst.*, Oct., 1967, *125*, 725–729. (From: Royal Prince Alfred Hospital and Department of Medicine, Nuclear Medicine, University of Sydney, Sydney, Australia.)

Liver scanning can never replace careful clinical appraisal in the assessment of suspected hepatic trauma, but it can provide information which is not available with current roentgenologic techniques.

The procedure of photoscanning with colloidal radioactive gold is simple, relatively atraumatic, and accurate. Each 100 microcuries delivers a dose of only 4 rads to the liver, and no liver damage has been found. Lesions 3 to 5 cm. in diameter have been detected.

The presence of a normal convex outline of the upper surface of the right lobe is especially useful in excluding extensive subphrenic collections from any cause.

Serial scans can provide a record of repair and regeneration.—*Arch H. Hall, M.D.*

Woodbury, David H., and Beierwaltes, William H. Fluorine-18 uptake and localization in soft tissue deposits of osteogenic sarcoma in rat and man. *J. Nuclear Med.*, Sept., 1967, *8*, 646–651. (From: Department of Internal Medicine [Nuclear Medicine], University of Michigan Medical Center, Ann Arbor, Mich.)

Fluorine 18 has been demonstrated to concentrate in the region of metastases to bone, and also in the region of primary bone tumors. The authors undertook to determine whether this radionuclide, given as the fluoride, could be used to scan soft tissue metastases from osteogenic sarcoma.

The authors first studied a mature rat who had developed a spontaneously occurring osteogenic sarcoma. The tumor was transplanted to several soft tissue sites, and 1 mc fluorine 18 was given. The animal was scanned, directional counts were made over the primary tumor, the metastases and a number of body sites, and the soft tissue tumors were then excised for histologic study. Some of the slides were prepared for autoradiography. F^{18} was found to localize in the soft tissue tumor transplants in this animal, and there was evidence of the presence of a good deal of radioactive fluoride between and about the malignant tumor osteoblasts.

An 18 year old man presented himself for study after he had undergone a right lower extremity amputation for osteogenic sarcoma. When tested by the authors he had evidence of multiple metastatic lesions in the lung. A dose of 1.5 mc of F^{18} was given by intravenous injection and 1 hour later posterior and anterior scannings of the chest were performed. These showed sharp and definite localization of F^{18} within metastatic lesions, suggesting that this agent might be used to detect early metastatic lesions in planning the treatment for primary osteogenic sarcomas.—*Frederick J. Bonte, M.D.*

Yeh, Shin-Hwa, and Kriss, Joseph P. Distribution and scintiphotography of a new complex, pentavalent technetium-99m citrate: studies in the rodent. *J. Nuclear Med.*, Sept., 1967, *8*, 666–677. (From: Division of Nuclear Medicine, Department of Radiology,

Stanford University School of Medicine, Palo Alto, Calif.)

The authors prepared a pentavalent Tc^{99m} citrate complex by reducing pertechnetate with ascorbic acid in the presence of thiocyanate, and thereafter forming the complex by a substitution reaction with citrate and Tc^{99m} thiocyanate complex. The citrate complex was identified by chromatography. Distributions of the Tc^{99m} citrate complex were carried out in mice and rats, and compared with the distribution of the same radionuclide as pertechnetate. Various organs were sampled and the data were expressed as percentage of injected dose. A parallel distribution study was carried out by means of scintiphotographs made at intervals after injection of each of the emitters.

Both of the distribution studies showed clear and specific localization of the Tc^{99m} citrate complex in the urinary tract, suggesting that this compound might be a potential agent for scanning the kidneys in humans.

The authors feel that citrate toxicity will not be a limiting factor. The critical organ with Tc^{99m} citrate complex is the kidney. In the rat a dose of 500 μc/kg. gave a renal absorbed radiation dose of only 0.2 mrad.

The agent deserves further study as a renal scanning tracer.—*Frederick J. Bonte, M.D.*

ROSENTHALL, LEONARD. Visualization of the bone marrow with technetium-99m sulfur colloid. *J. Canad. A. Radiologists*, Sept., 1967, *18*, 407–411. (From: Department of Radiology, Montreal General Hospital, Montreal, Quebec, Canada.)

The bone marrow has been studied by means of scintillation scanning with a number of tracer agents. Fe^{59} emits gamma photons of an energy too high (1.1 and 1.29 mev.) for effective collimation. A number of colloids, principally Au^{198} have been used in the past. The 2.5 mc tracer dose of colloidal radiogold which is usually employed delivers a high marrow absorbed dose of from 7 to 18 rads. Newer agents include colloidal indium 113m and technetium 99m sulphur colloid. The author prefers the latter agent, and after preparing it by the method of Patton *et al.*, administers it in tracer doses of 5 mc. Scanning is begun one-half hour after tracer administration and scintiphotos are made with a large-crystal scintillation camera. Premedication with 250 mg. of potassium perchlorate is given to prevent the uptake of free Tc^{99m} by the thyroid gland.

The author shows a normal study of pelvic marrow, and presents 5 examples of marrow replacement by tumor. He shows a case in which marrow activity is definitely reduced within the bony pelvis as the result of prior radiation therapy. A final case illustrates expansion of the bone mar[illegible] with hemolytic anemia.

Technetium 99m sulphur colloid appears [illegible] a satisfactory agent to scan the marrow wi[illegible]ed patient radiation dose.—*Frederick J. B[illegible] M.D.*

COBAU, CHARLES D., SIMONS, [illegible]LES S., and MEYERS, MURIEL C. Accidental overdosage with radiophosphorus: therapy by induced phosphate diuresis. *Am. J. M. Sc.*, Oct., 1967, *254*, 451–463. (From: The Department of Internal Medicine and Radiology, The University of Michigan School of Medicine, Ann Arbor, Mich.)

This is a report of an accidental overdosage in the administration of radioactive phosphorus 32 because the stock solution was labelled incorrectly with 9 instead of 10 used to designate the month of October. As a result of this error, 16.2 rather than 4.05 mc of P^{32} was administered orally. The error was discovered so that on the ninth post-treatment day the patient was admitted for observation and an attempt to induce phosphate diuresis.

The hematologic consequences followed closely the course anticipated on the basis of previous studies of the effects of ionizing radiation. Between the ninth and the thirteenth day a fall in the counts of all blood cells was observed. Thereafter these counts fluctuated at depressed levels until the recovery phase which was observed during the second month after P^{32} administration.

Because of the likelihood of the anticipated bone marrow dose of 954 rads resulting in permanent and fatal hypoplasia of the bone marrow, an attempt was made to increase elimination of the isotope in the urine through induction of phosphate diuresis by administration of stable phosphorus, calcium gluconate and parathormone. Subsequent analyses of the excretion of P^{32} showed a decrease in the effective half-life from 11.2 to 4.8 days, equivalent to a seven fold increase in the rate of isotope excretion. As a result, the anticipated exposure to the bone marrow was reduced by 38 per cent. By the 165th day following exposure, the patient had recovered fully from the immediate hematologic effects of excessive radiation exposure.—*Merle K. Loken, Ph.D., M.D.*

CHEMOTHERAPY

SULLIVAN, ROBERT D., MILLER, EDWARD, ZUREK, WLADYSLAW Z., OBERFIELD, RICHARD A., and OJIMA, YOICHI. Re-evaluation of methotrexate as an anticancer drug. *Surg., Gynec. & Obst.*, Oct., 1967, *125*, 819–824. (From: The Departments of Cancer Research and of Internal Medicine, Lahey Clinic Foundation, Boston, Mass.)

Me[illegible] was [illegible]ginally used to produce t[illegible] [illegible]sions of acute leukemia in children. [illegible] s[illegible]id t[illegible]mors was disappointing. One reason [illegible] [illegible]e s[illegible]hedule—5 mg. per day orally or [illegible] Excretion of the drug in 4 to 8 hours [illegible] s[illegible] a transient antimetabolic effect. To [illegible] [illegible]ect, 5 mg. per day was given either in [illegible] intravenous infusion per 24 hours for [illegible] patients or in 4 equal oral doses of 1.25 [illegible] was continued on a daily basis until signs [illegible] to[illegible]ity appeared—usually in 5 to 10 days. Man[illegible]ations of toxicity usually disappear within 4 to [illegible] ays. Repeated courses of therapy are then given [illegible]g as evidence of improvement persists.

[illegible] hundred sixty-one patients with various [illegible] of solid tumors were treated with approximately 30 per cent objective tumor response being obtained. This was characterized by regression of 50 per cent or more of all measurable disease associated with clinical benefit and maintained for a period of at least 2 months. Duration of remission varied from 2 to 15 months and averaged 4.4 months. The therapeutic activity of methotrexate in solid tumors compares favorably with other cancer chemotherapeutic compounds currently in use.—*John Thomas McMurray, M.D.*

MISCELLANEOUS

HODGKINSON, A., NORDIN, B. E. C., HAMBLETON, JOAN, and OXBY, C. B. Radiostrontium absorption in man: suppression by calcium and by sodium alginate. *Canad. M. A. J.*, Nov., 4, 1967, *97*, 1139–1143. (Address: A Hodgkinson, Assistant Director, Medical Research Council, Mineral Metabolism Unit, The General Infirmary, Leeds, York, England.)

Intestinal epithelium preferentially absorbs calcium more efficiently than strontium or barium. This biologic discrimination must be enhanced to prevent the absorption of appreciable quantities of radiostrontium from contaminated foodstuffs.

It has been shown that the intestinal absorption of radiostrontium in man is inversely related to the dietary intake of calcium and is inhibited by orally administered sodium alginate. Sodium alginate also inhibits the absorption of radiocalcium but to a lesser extent than radiostrontium. Measurements of fecal magnesium, iron, copper, and zinc indicate that sodium alginate also inhibits the absorption of these metals.

When the sodium alginate was given 30 minutes b[illegible]fore the is[illegible]topes, plas[illegible] r[illegible]duc[illegible], [illegible] maximum in[illegible] [illegible] take was observed whe[illegible] [illegible]ministered simultaneousl[illegible] [illegible] [illegible]ffinity of sodium alginate for [illegible] calcium, and magnesium decrease[illegible] Fe > Sr > Ca > Mg. It was concluded [illegible] of metallic irons by sodium algina[illegible] [illegible]ion exchange mechanism, with the bindin[illegible] [illegible]dent upon pH, being virtually abolished below [illegible]—*Donald M. Monson, M.D.*

HESLOP, R. W., OAKLAND, D. J., and MA[illegible]OX, B. T. Ultrasonic therapy in Peyronie's disease. *Brit. J. Urol.*, Aug., 1967, *39*, 415–419. (From: The Departments of Urology and Physiotherapy, Queen Elizabeth's Hospital, Birmingham 15, England.)

A one megacycle per second ultrasonic beam has been used to treat 9 cases of Peyronie's disease. Duration of therapy ranged from 6 treatments over 1 month to 42 treatments in 2 courses of 1 month each. Each application lasts 10 minutes and during this time the applicator is moved over and around the plaque continuously so that the beam passes through the plaque in the shaft of the penis at various angles. The variation in the angle of the beam produced by moving the applicator head is important as considerable heat may be generated at the point of exit of the beam and in 1 case superficial blistering occurred 24 hours after the first application.

The administered beam in current use is a non-pulsed beam of 3 watts/cm.^{2} intensity. Thyxotropine "P" ointment is applied to the penis as a coupling medium.

The results obtained in this series compare with those of other reported series in that irrespective of the treatment given, approximately 2/3 of men with Peyronie's disease were able to resume intercourse. Furthermore, these results compare closely with the untreated group reported by Ashworth (1960) in whom 6 of the 8 patients had resumed intercourse although with diminished satisfaction.

The authors found that early relief of pain was achieved in all patients after a short course of ultrasonic therapy.

Ultrasonic therapy proved extremely simple to administer on an out-patient basis and all patients showed marked psychologic improvement. By its very simplicity ultrasonic therapy seems to have material advantages over radiotherapy, surgery, steroid therapy or other drug administration.—*David A. Lightfoot, M.A.*

SUBJECT INDEX TO VOLUME 1 2

(E) = editoria (ab) = abstract

AUTHOR INDEX TO VOLUME 102

*=original article

Although your pr nt x-r
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requirements, it is quite possib
ray tube is often overloaded as a result of
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imes, create a condition which requires greater x-ray tube
capacity.

■ Anticipating this escalation in x-ray exposures, Machlett has increased the thermal capacity of all rotating anode ray be from the Dynamax "HD25" to the Dynamax
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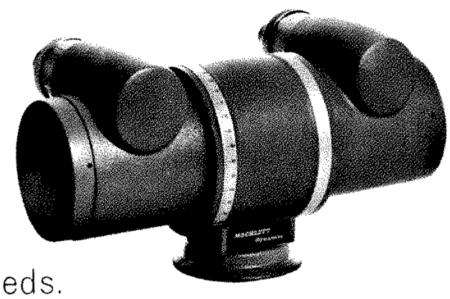

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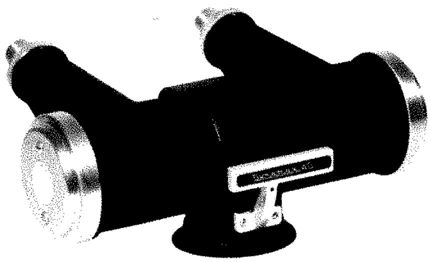

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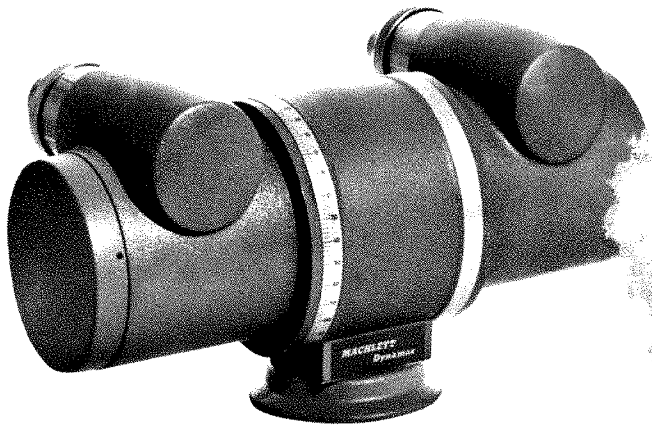

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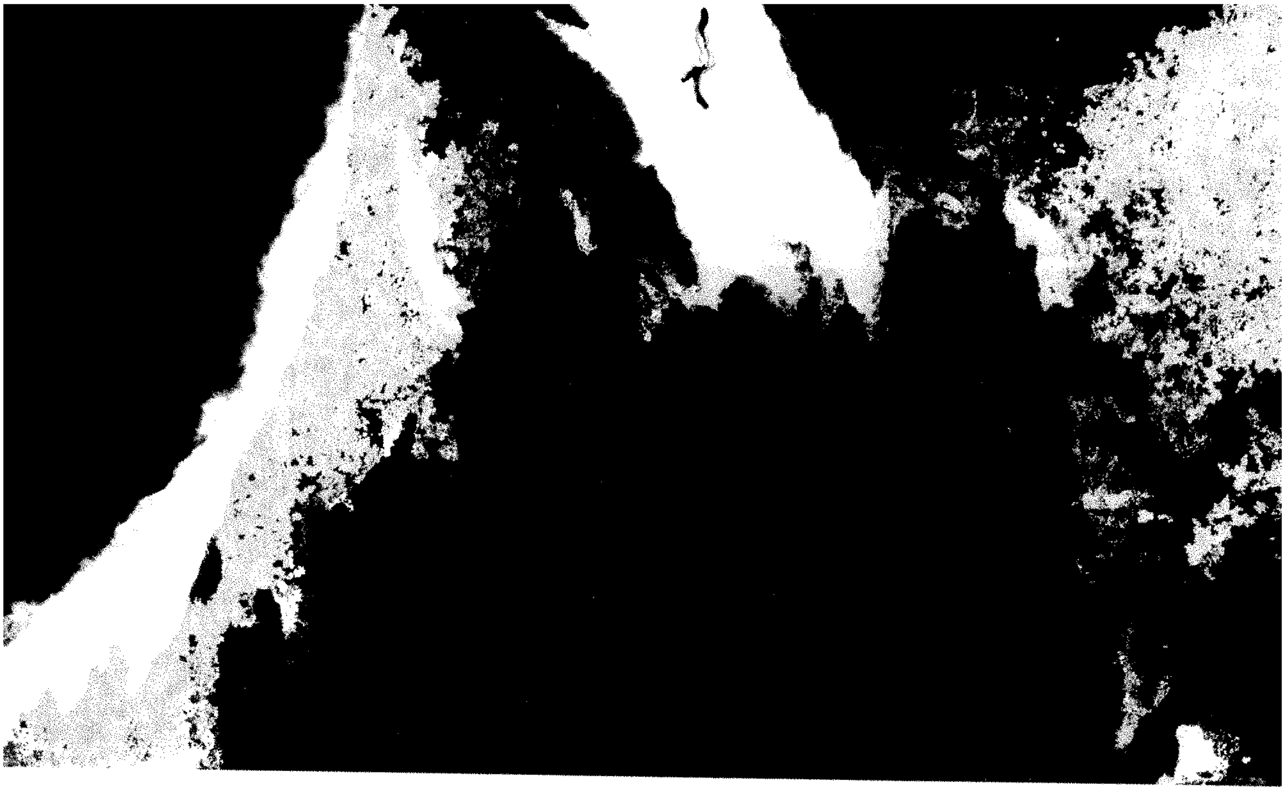

[illegible] y means greater utilization of examination rooms and equipment . . . dry, ready-to-read film 90 seconds after the conclusion of the examination . . . significant speeding up of examinations that require processed films during the procedure . . . improved flow of "doctor-ready" patients.

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1. As published in the September, 1967, JOURNAL OF THE CANADIAN ASSOCIATION OF RADIOLOGISTS, Vol. XVIII, pages 389-392. For your copy of the full report, write: Eastman Kodak Company, Radiography Markets Division, Rochester, N.Y. 14650, or contact your Kodak Technical Sales Representative.

. . . to the patient, hospital, and technologist

Kodak's 90-second processing system is meaningful to the patient, too. For one thing, he benefits from the better, quicker, more efficient care the radiological team can render. He can be released without the need for call-backs because it is possible to make adequacy checks immediately following exposure. Anesthesia time during special procedures, radiologists report, can often be shortened. Also, it has been reported that treatment, in some cases, can be started sooner.

The hospital and the radiologist with an office practice profit because greater efficiency means greater economy. And, most important, space is more productively used because of greater processing volume.

The technologist becomes more efficient working with the Kodak 90-second processing system. Immediate film access reduces film loss or misplacement. Quality improves because technic can be checked before the patient leaves the room; finished radiographs can be correlated with the technic used. And there's no time loss and confusion of a processing backlog. (Only 6½ minutes are required to process a 20-film, 14 [illegible] series in a *Kodak* RP *X-Omat* Processor, Model M6.)

How do y[illegible]

Installing a 90-sec[illegible] Kodak RP *X-Omat* System is [illegible] dering the compac[illegible] *X-Omat* Processor, Mod[illegible] first processor designed [illegible] second proce[illegible] less than 5 [illegible] [illegible]

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is retractable and the treatment couch is easily remo...

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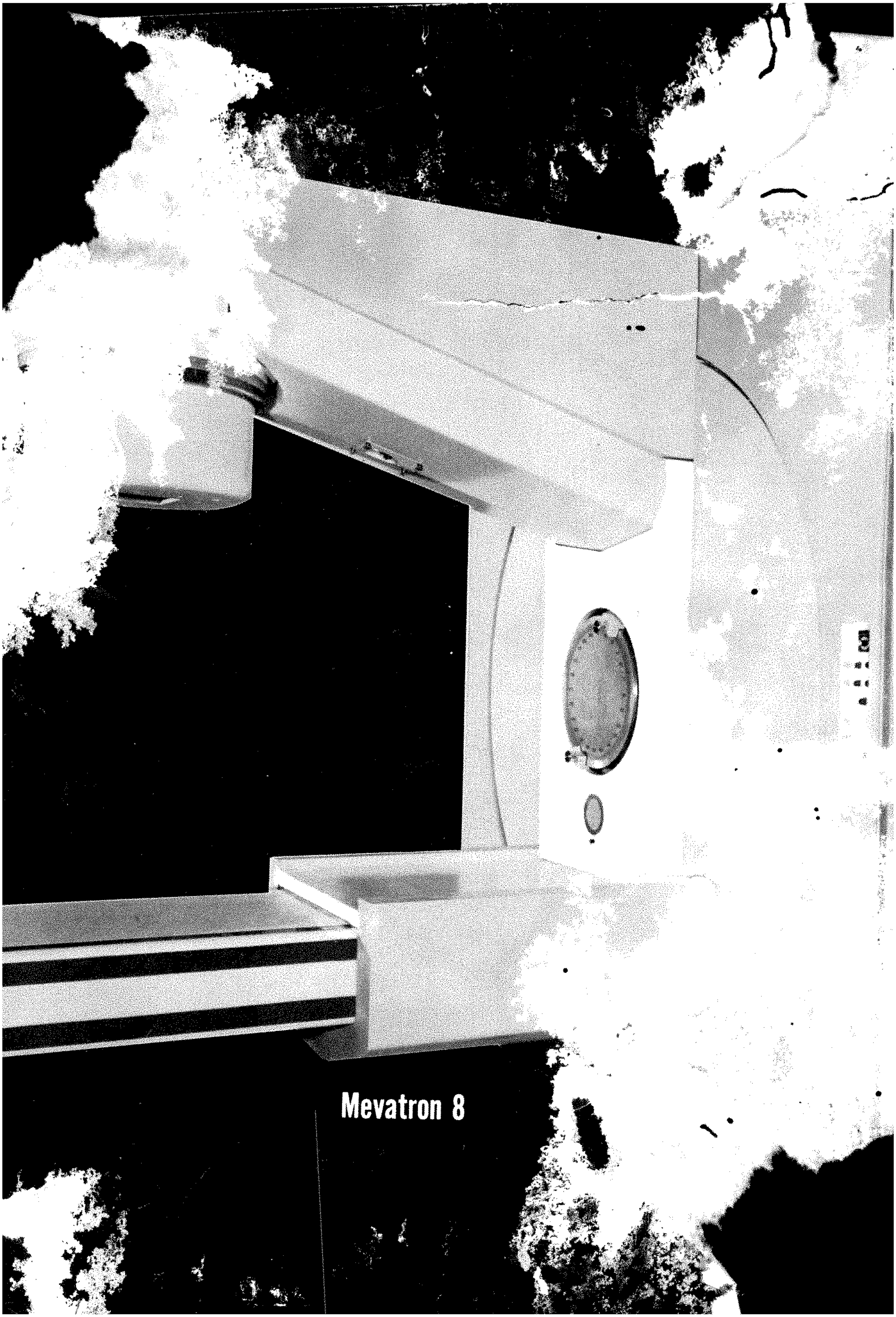
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(Too demanding of information to sacr... i... quality for the sake of speed. And vice versa.

To date the Radiois... a large patient load a... he... maximum information ... really had only two kinds ... either (1) good images, s... or more recently (2) higher ... expense of picture quality. But s... neither choice is quite appropria... need, there now comes a third option, the Dynapix. Design goals: *maximum information/minimum time*. Is this actually possible? Isn't compromise inevitable?

A totally new approach obviated the need for compromise. The Dynapix is a completely unique radioisotope imaging device which has, among other things, ten (10!) scintillation detectors working in concert, each detector with its own focusing collimators, each detector with its own electronics.

The practical import of this?

High speed

Since each of the ten scintillation detectors has its own electronics, the whole assembly can count many times faster than a single detector of *any* size. There is no faster detection system now

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... least 2½ times larger
than that of other high-speed instruments
and has no distortion at the edges.

Other important features, briefly

(1) Three types of data readout provide maximum flexibility: TV screen, Polaroid camera (positive or negative film), and scaler.

(2) Magnetic tape storage of *total* data for rapid playback at variable data enhancement settings.

(3) Easy to use: experienced workers in this field can be getting usable Dynapix scans on the day of installation.

(4) The Dynapix produces pictures which are familiar and can be easily related to one's prior experience.

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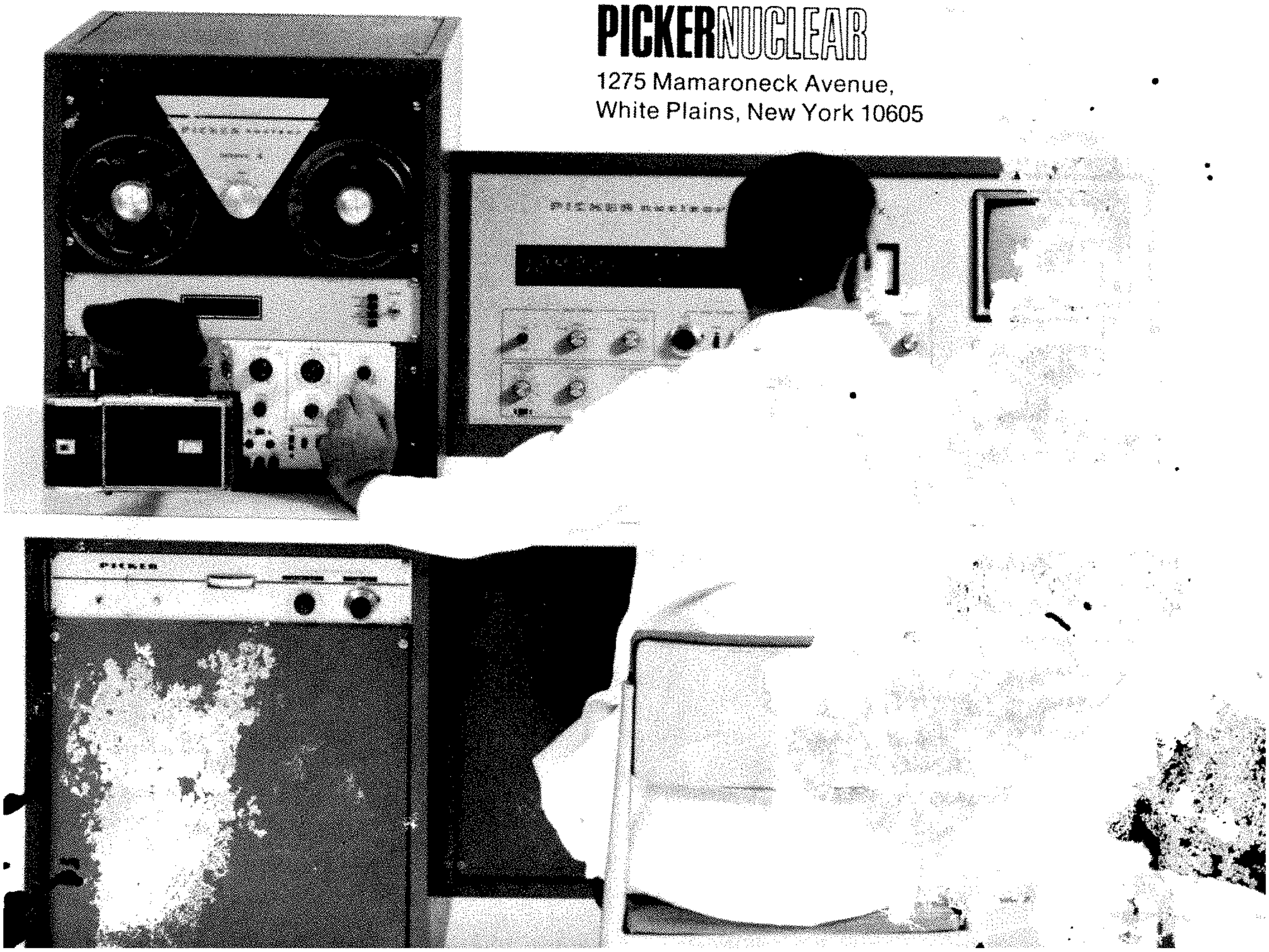
The Dynapix has been proven in major clinical installations. This enables us to provide proof of the many claims above. Accordingly, the object of this entire presentation is to solicit such challenges, and to leave you with the simple message: Dynapix provides *maximum information* in *minimum time:* Now demand proof by requesting data file 114X



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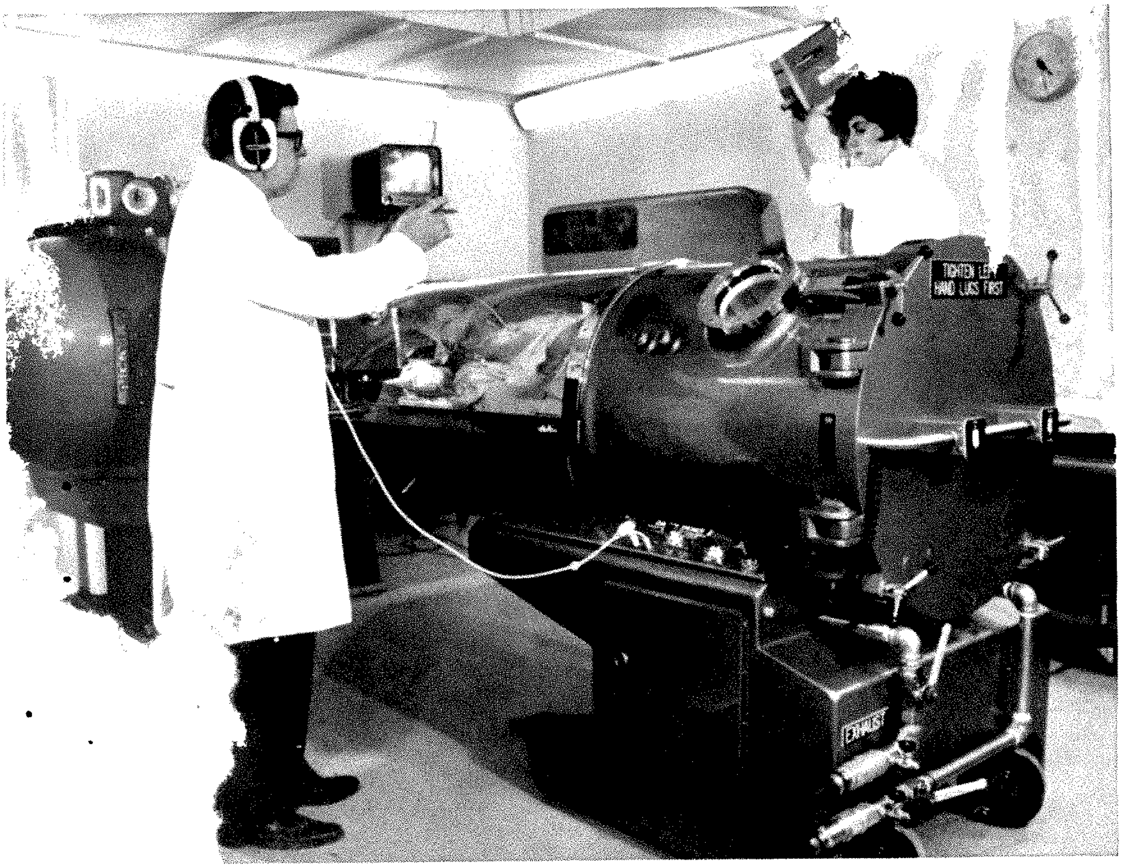

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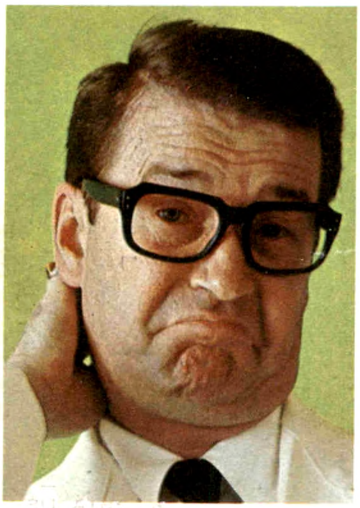

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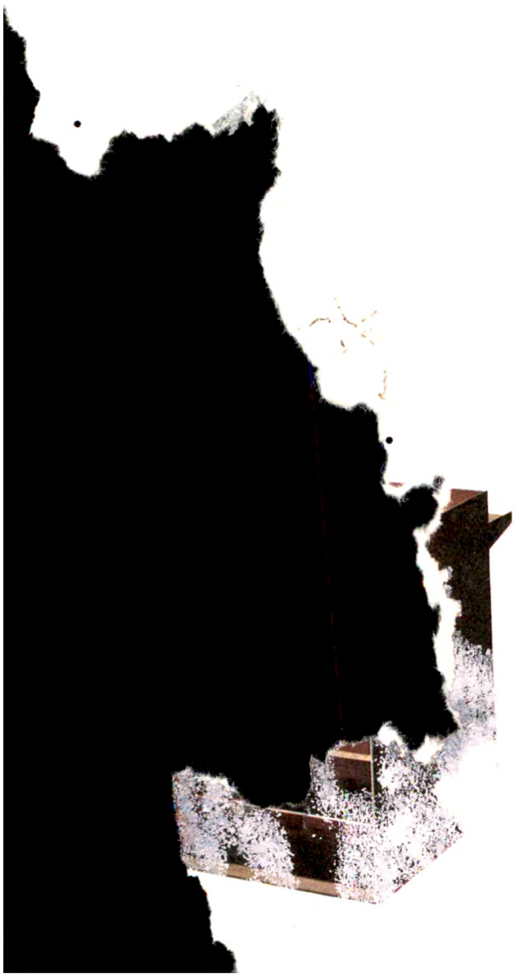

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...Effects: Such agents may produce symptoms of an anaphylactic nature in sensitive... ...ld be watched carefully during injection as serious reactions, including fatalities,... ...ed media. Although allergic reactions generally occur quickly, occasio... ...ifeste... for 10 or even 15 minutes. Warning signs and symptoms of possible intole... ...ratory difficulty (wheezing, dyspnea or sensation of suffocation, and tightness... ...zing, itching or urticaria, nausea or vomiting, and fainting. Minor reactions, ...sive salivation, flushing, dizziness, urticaria, and muscular twitching may occ... in persons with a history of bronchial asthma or other allergic manifestations o... ...e. Infrequently "iodism" (salivary gland swelling) from organic compounds... exposure and subsides by the sixth day.

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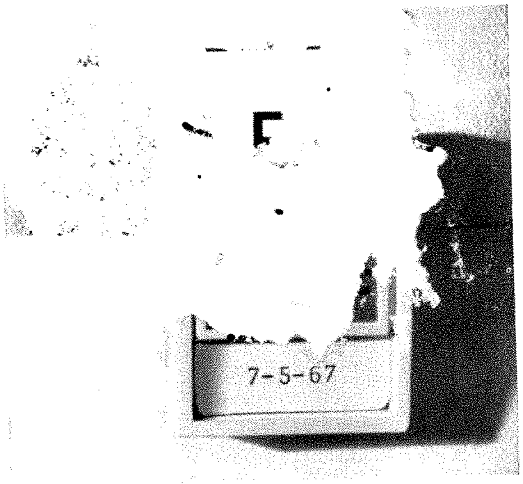

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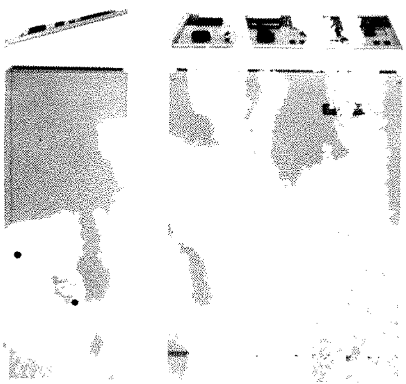

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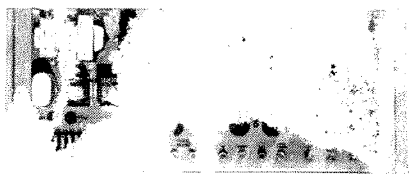

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